LOW T3 SYNDROME IN CHRONIC HEART FAILURE- PREVALENCE AND PROGNOSTIC SIGNIFICANCE

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CERTIFICATE

This is to certify that the dissertation titled **"Low T3 syndrome in chronic heart failure : Prevalence and Prognostic Significance"** is the bonafide original work of **DR.SHARADHA.S** in partial fulfilment of the requirements for **M.D. Branch I General Medicine** Examination of the Tamilnadu DR. M.G.R Medical University to be held in April 2018. I forward this to the DR. M.G.R Medical University, Chennai, Tamilnadu, India.

PROF.DR.S.TITO MD
Professor of Medicine
Institute of Internal Medicine
Madras Medical College
Government General Hospital,
Chennai-600 003.

PROF.DR.S.MAYILVAHANAN MD
Director
Institute of Internal Medicine
Government General Hospital
Chennai-600 003

PROF.DR.R. NARAYANABABU M.D.,DCH.,
Dean, Madras Medical College,
Government General Hospital,
Chennai-600 003

DECLARATION

I, **DR.SHARADHA.S**, solemnly declare that dissertation titled **"Low T3 syndrome in chronic heart failure : Prevalence and Prognostic Significance"** " is a bonafide work done by me at Madras Medical College & Government General Hospital, Chennai during 2017 - 2018 under the guidance and supervision of **Prof. Dr. S. TITO M.D.**

This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University towards part fulfilment of requirements for the award of **M.D. Degree (Branch – I) in General Medicine.**

Place: Chennai.
Date:

Dr.SHARADHA.S
Postgraduate Student
M.D General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai

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ABBREVIATIONS

ACC/AHA	-	American college of cardiology/American heart association
CAD	-	Coronary Artery Disease
CHOD	-	Cholesterol Oxidase
ECHOES	-	Echocardiographic Heart of England Sreening study
EF	-	Ejection Fraction
HDL	-	High Density Lipoprotein
HF	-	Heart Failure
LV	-	Left Ventricle
LDL	-	Low Density Lipoprotein
LVEDD	-	Left Ventricular End Diastolic Diameter
LVESD	-	Left Ventricular End Systolic Diameter
MONICA	-	Monitoring of trends in and determinants of mortality from cardiovascular disease
NHANES I	-	First National Health And Nutritional Examination Survey
PAP	-	Peroxidase,4-Aminoantipyrine and Phenol.
rT3	-	reverse Triiodothyronine
T3	-	Triiodothyronine
T4	-	Thyroxine
TSH	-	Thyroid Stimulating Hormone
TRH	-	Thyrotrophin releasing Hormone
TGL	-	Triglyceride
VLDL	-	Very Low Density Lipoprotein

INTRODUCTION

INTRODUCTION

Thyroid hormone has a fundamental role in the cardiovascular homeostasis, both in physiological and pathological conditions. Changes in peripheral thyroid hormone concentration and metabolism can occur in euthyroid patients suffering from heart failure. In heart failure the main alteration of the thyroid function is referred to as low-T3 (triiodothyronine) syndrome or euthyroid sick syndrome, characterized by the reduction in serum total T3 and free T3 with normal levels of thyroxine and thyrotropin. This low-T3 syndrome has commonly been interpreted as an adaptive compensatory and beneficial response that decreases energy consumption in diseased states but this view is now being challenged.

Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorders that impairs the ability of ventricles to fill with or eject blood[1]. Coronary artery disease accounts for a substantial portion of patients with chronic heart failure.

Survival is markedly shortened in patients with heart failure. The overall 5-year mortality for all patients with heart failure is approximately 50 percent and the 1-year mortality in patients with end stage heart failure may be as high as 75 percent[2].

The role of various biological and neurohormonal factors in risk stratification of chronic heart failure has been studied in various clinical trials. Noradrenaline**,** angiotensin II, Atrial natriuretic peptide (ANP) and Brain natriuretic peptide (BNP) are used as important prognostic markers in patients with heart failure[3].Recent studies have explored the use of triiodothyronine levels to predict mortality in heart failure patients.

Studies suggest that low T3 (triiodothyronine) levels correlate with increased mortality in chronic heart failure patients and benefits can be gained from thyroid hormone supplementation[4,5].

AIM OF THE STUDY

AIM OF THE STUDY

- To estimate the prevalence of low-T3 (triiodothyronine) syndrome in chronic heart failure
- To assess the role of T3 as an adjunct to clinical and functional parameters when estimating morbidity and mortality in patients with chronic heart failure.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

In the past decade, progress in the understanding of heart failure has proceeded at an unprecedented rate. Scientific discovery and development in fields as disparate as epidemiology and molecular biology, has provided profound insights into the mechanism and treatment methods of heart failure.

DEFINITION OF HEART FAILURE

In 1933, Thomas Lewis defined heart failure as "A condition in which the heart fails to discharge its contents adequately".

The Task Force of the European Society of Cardiology[6] in 1995 stated diagnosis of heart failure consists of "Symptoms of heart failure, objective evidence of cardiac dysfunction and response to treatment directed towards heart failure".

The most accepted and practical definition of heart failure appeared in 2001 ACC/AHA guidelines[7] for the evaluation and management of chronic heart failure in adults, which states “Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorders that impairs the ability of ventricles to fill with or eject blood”.

Heart failure is a clinical syndrome that is characterized by specific symptoms (dyspnea and fatigue) in the medical history and signs (edema, rales) on the physical examination. There is no single test for heart failure because it is largely a clinical diagnosis that is based on careful history and physical examination. Because not all patients have volume overload at the time of initial or subsequent evaluation the term heart failure is preferred over the older term "congestive heart failure".

Definition of Heart Failure

Classification	Ejection Fraction	Description
I. Heart Failure with Reduced Ejection Fraction (HF*r*EF)	≤40%	Also referred to as systolic HF. Randomized clinical trials have mainly enrolled patients with HF*r*EF and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart Failure with Preserved Ejection Fraction (HF*p*EF)	≥50%	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, Borderline	41% to 49%	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patient with HF*p*EF.
b. HF*p*EF, Improved	>40%	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

Framingham criteria for HF

Major criteria

- Paroxyzmal nocturnal dyspnoe
- Neck-vein distension
- Rales
- Cardiomegaly
- Acute pulmonary edema
- S3 gallop
- ↑ venous pressure(16 cm H_2O)
- Hepatojugular reflux
- Loss of weight > 4,5 kg during 5 days

Minor criteria

- Ankle edema
- Night cough
- Dyspnoe on exertion
- Hepatomegaly
- Pleural effusion
- Tachyaardia (>120/min.)

2 major or 1 major plus 2 minor criteria are needed for the diagnosis of heart failure

EPIDEMIOLOGY OF HEART FAILURE

Worldwide, heart failure affects nearly 23 million people.th prevalence of HF increases exponentially with age and increases from 0.4 in the middle age to 4-8% in persons older than 65 years.

The Framingham heart study[8] has been the most important longitudinal source of data on the epidemiology of heart failure. The

prevalence of HF 7.4/1000 in males, 7.7/1000 in females. The annual incidence of HF per 1000 population is 2.3 in males and 1.4 in females.

The reported incidence of heart failure for patients with CHD ranges from 0.4% to 2.3% per year, suggesting that about one to six lakhs of Indians could develop symptomatic heart failure. Given the fact that cardiovascular disease is currently the leading cause of death in India, the projected numbers are expected to rise.[74]

The International Congestive Heart Failure (INTER-CHF) study aimed to measure mortality at 1 year in patients with heart failure in Africa, China, India, the Middle East, southeast Asia and South America and explored demographic, clinical, and socioeconomic variables associated with mortality. The mortality in India was 23% at one year, second only to Africa (34%).[75]

Acute heart failure is defined as the new onset or recurrence of symptoms and signs of heart failure requiring emergent therapy and resulting in seeking unscheduled care or hospitalisation.. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and afterload mismatch. Other overlapping terminologies used are

ADHF (acute decompensated heart failure), ADCHF(acute decompensation of chronic heart failure),HHF(hospitalisation for heart failure),etc.

Chronic heart failure develops and progresses slowly. LV dysfunction begins with injury or stress to the myocardium and is a progressive process. This progression leads to change in geometry and structure of LV such that the chamber dilates or hypertrophies, a process termed cardiac remodelling. Cardiac remodelling contributes substantially to progressive worsening of heart failure .The course of development of heart failure is classified into 4 stages.

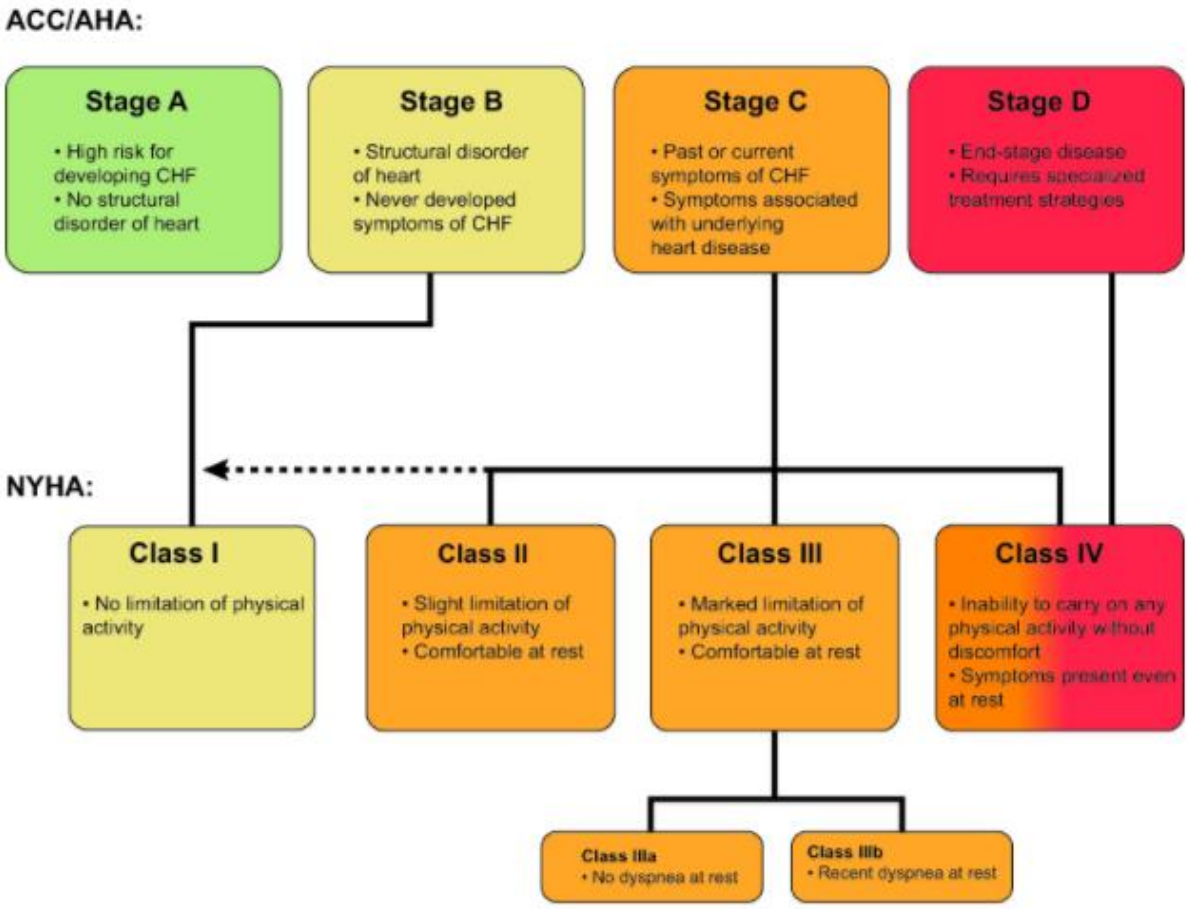
STAGES OF CHRONIC HEART FAILURE[9]

STAGE A. AT HIGH RISK FOR HEART FAILURE – conditions strongly associated with development of heart failure. No identifiable structural or functional abnormalities of pericardium, myocardium or cardiac valves. No history of signs and symptoms of heart failure.

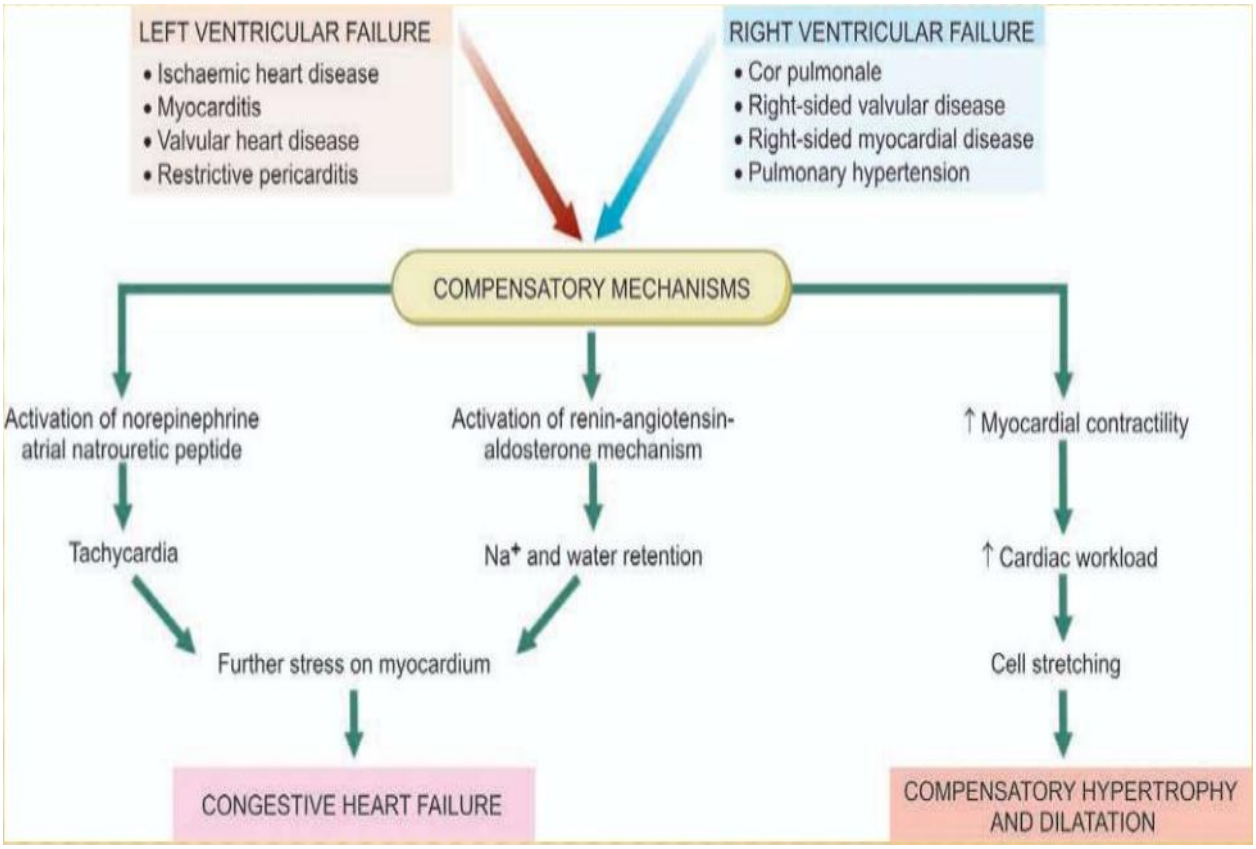
STAGE B. STRUCTURAL HEART DISEASE BUT WITH OUT SIGNS AND SYMPTOMS OF HEART FAILURE

STAGE C. CURRENT OR PRIOR SYMPTOMS OF HEART FAILURE ASSOCIATED WITH UNDERLYING STRUCTURAL HEART DISEASE

STAGE D. ADVANCED STRUCTURAL HEART DISEASE AND MARKED SYMPTOMS OF HF AT REST DESPITE MAXIMAL MEDICAL THERAPY. REQUIRE SPECIAL INTERVENTIONS



Pathophysiology of heart failure :



ETIOLOGY OF CHRONIC HEART FAILURE

Impairment of left ventricle function accounts for majority of symptoms in heart failure. Coronary artery disease, hypertension and dilated cardiomyopathy accounts for substantial proportion of heart failure. Valvular heart disease and anemia are common causes of HF in Indian population. Arrhythmias, pericardial diseases, shunts and thyrotoxicosis are other less common causes.

Worldwide CAD accounts for two thirds to three fourths of the causes of HF. In NHANES I epidemiological follow-up study[10] coronary artery disease was the major cause of HF in 61.1% of patients. The Glasgow group of the MONICA study and the ECHOES Group have found that coronary artery disease is the most powerful risk factor for impaired left ventricular function and HF.

Advancing age, Hypertension, Diabetes Mellitus, Smoking and Obesity also form major risk factors for heart failure. Sex based differences were noted in the causality, with hypertension playing the major role in women and CAD in men. Although obesity is a risk factor for HF, obese patients with HF seem to have a better clinical outcome and this has been called the " obesity paradox".

ETIOLOGY OF HEART FAILURE

Myocardial disease
Coronary artery disease
Myocardial infarction*
Myocardial ischemia*
Chronic pressure overload
Hypertension*
Obstructive valvular disease*
Chronic volume overload
Regurgitant valvular disease
Intracardiac (left-to-right) shunting
Extracardiac shunting
Nonischemic dilated cardiomyopathy
Familial/genetic disorders
Infiltrative disorders*
Toxin/drug-induced damage
Metabolic disorder*
Viral or other infectious agents
Disorders of rate and rhythm
Chronic bradyarrhythmias
Chronic tachyarrhythmias
Pulmonary heart disease
Cor pulmonale
Pulmonary vascular disorders
High-output states
Metabolic disorders
Thyrotoxicosis
Nutritional disorders (beriberi)
Excessive blood flow requirements
Systemic arteriovenous shunting
Chronic anemia

*Condition(s) that also can lead to HFpEF.

CORONARY ARTERY DISEASE AND CHRONIC HEART FAILURE

Several factors contributing to LV dysfunction and hence symptoms of chronic heart failure in coronary artery disease. Almost 50% of patients surviving myocardial infarction develop heart failure.

Loss of functioning myocytes and myocardial fibrosis following acute myocardial infarction leads to LV remodelling and chamber dilatation. Significant atherosclerotic disease in coronary arteries other than the infarct-related artery and neurohormonal activation lead to progressive dysfunction of the remaining viable myocardium. In addition recurrent myocardial infarction may produce future deterioration of LV function.

Exertion superimposes ischemia on the ventricle with irreversibly damaged myocardium, which may cause prolonged systolic dysfunction that persists even after the ischemic insult itself has resolved. This phenomenon is termed exercise-induced "stunning,"[11] and has been shown to be associated with progression of LV dysfunction.

Myocardial “hibernation” refers to adaptive response to sustained reduction in myocardial blood flow, in which the level of tissue perfusion

is sufficient to maintain cellular viability but insufficient for normal contractile function, further compromising LV function.[12.]

The baroreceptor mediated activation of sympathetic nervous system[13] that occurs with ventricular dysfunction leads to vasoconstriction, tachycardia, increased contractility, increased preload and after load. Increased local and systemic levels of norepinephrine induce apoptosis and is directly toxic to the myocytes.

The activity of renin angiotensin aldosterone system is increased in patients with heart failure. Raised angiotensin II and aldosterone levels have a mitogenic effect on cardiac myocytes with resultant LV remodelling. Chronic neurohormonal activation affects myocyte growth, interstitial connective tissue, myocardial energy utilization, and receptor regulation further detoriating LV function.

SYSTOLIC AND DIASTOLIC HEART FAILURE

In chronic ischemic heart disease systolic heart failure (heart failure with reduced ejection fraction HFrEF) is caused by both the chronic loss of contracting myocardium secondary to prior myocardial infarction and the acute loss of myocardial contractility induced by transient ischemia. Diastolic heart failure (heart failure with preserved ejection fraction HFpEF) is due to ventricle’s reduced compliance caused

by replacement of normal, distensible myocardium with nondistensible fibrous scar tissue and by acute reduction of diastolic dispensability during ischemia.

The principle manifestation of systolic heart failure is due to inadequate cardiac output or salt and water retention or both. Diastolic heart failure leads to elevated ventricular filling pressures leading to pulmonary and systemic venous congestion.

ECHOCARDIOGRAPHY IN CHRONIC HEART FAILURE

The ACC/AHA guidelines recommend that, two-dimensional echocardiography should be performed during initial evaluation of patients presenting with HF to assess LV ejection fraction, LV size, wall thickness and valve function. It improves diagnostic accuracy and guides treatment of heart failure[14].

LV systolic function can be assessed by M-mode, 2-D and Doppler techniques. M-mode gives excellent resolution and measurement of LV dimensions and wall thickness.

2-D technique is used to measure LV volumes and ejection fraction. The LV is divided into 16 segments and an assessment of regional wall motion is made.

A segments systolic motion[16] is classified as

- Normal
- Hypokinetic (reduced movement)
- Akinetic (absent movement)
- Dyskinetic (movement in wrong direction)
- Aneurysmal (out pouching of all layers of the wall)

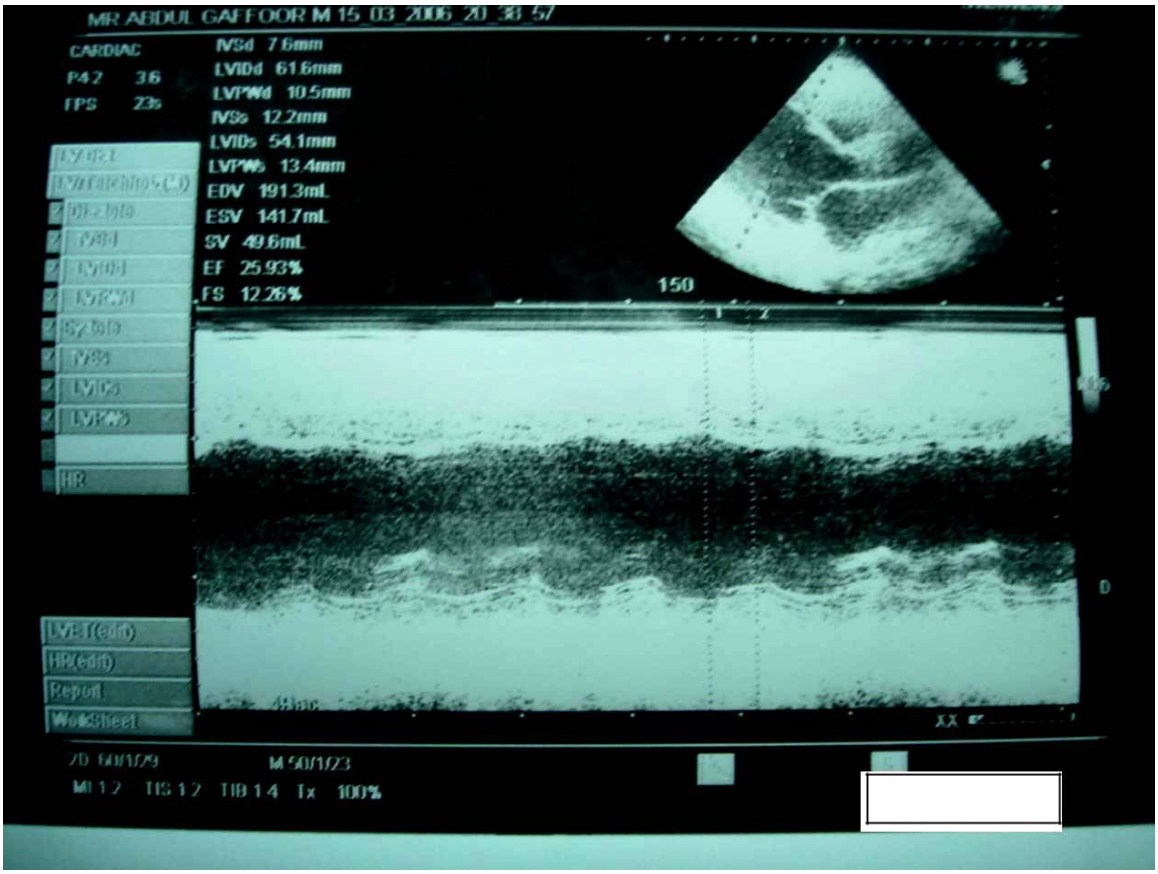
The echocardiographic evidence of regional wall motion abnormalities has been used in clinical diagnosis of coronary artery disease[17]. Presence of frank scars, aneurysm and any truly normally functioning segments point to the diagnosis of ischemic LV dilatation and dysfunction.

Doppler echo is useful in estimating the severity of mitral regurgitation and to measure pulmonary artery pressure using the gradient of tricuspid regurgitation.

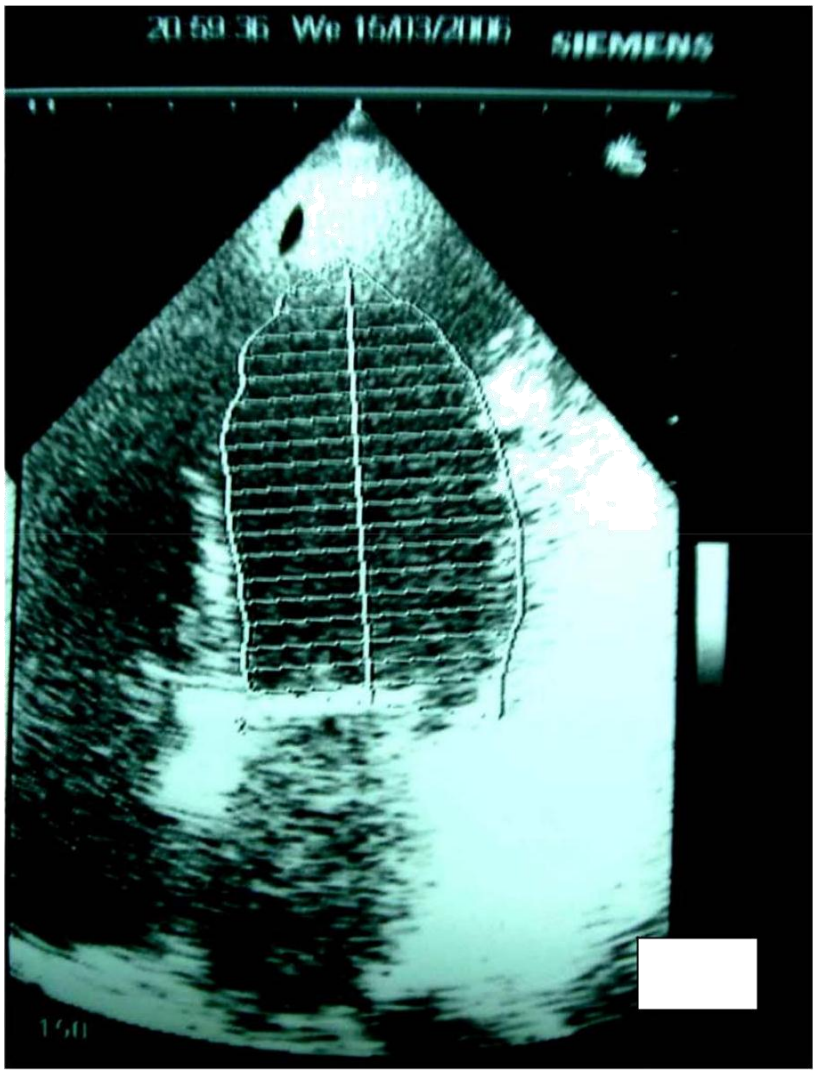
Coronary artery disease is the most common condition in which systolic and diastolic dysfunction coexists. Functional capacity appears related not only to systolic function, but also to diastolic function[18]. M-mode techniques have been used to record the rate of relaxation of ventricular cavity. Doppler echo[19] currently is the primary technique used for evaluating ventricular diastolic function. With normal pressures the

early diastolic mitral velocity (E) exceeds the following atrial systole or late mitral (A) velocity (E/A ratio greater than 1). Decreased LV relaxation due to diastolic dysfunction decrease in E velocity and increase in A velocity. The E/A ratio is less than 1 and the isovolumic relaxation time (IVRT) is prolonged.

Ejection Fraction (EF) measured by echocardiography is the most important measure of LV systolic function. Though MUGA scan can measure Ejection Fraction more accurately, the ability of echocardiography to measure valvular and wall motion abnormalities makes it a class I (definite evidence that it is useful and beneficial) investigation in initial evaluation of HF.



M MODE ECHO MEASUREMENT OF LV DIMENSION



2D ECHO SIMPSON'S METHOD FOR EJECTION FRACTION

Studies involving chronic heart failure use reduced ejection fraction as definite evidence of LV dysfunction. EF of less than 40% is used as a cut off in most of these studies.

RISK STRATIFICATION IN CHRONIC HEART FAILURE[6]

Risk stratification is prudent to determine the mortality and morbidity profile of patients with HF. It helps to identify patients who is at low risk and therefore can be managed medically. Invasive procedures should be reserved for patients at high risk of mortality.

The following parameters are strongly associated with increased mortality in chronic heart failure and are recommended in risk stratification.

- Advanced age
- Low serum sodium
- VO_2 max (mL/kg per min <10–14)
- Low LV ejection fraction[20]
- Resuscitated sudden death
- NYHA functional Class III–IV
- Persistent low BP
- High serum BNP[30,21]
- Increased left ventricular volumes
- High serum creatinine
- High serum bilirubin

TABLE 25-3 Prognostic Variables in Patients with Heart Failure

Demographics
Sex
Race
Age
Heart Failure Etiology
CAD
IDCM
Valvular heart disease
Myocarditis
Hypertrophy
Alcohol
Anthracyclines
Amyloidosis
Hemachromatosis
Genetic factors
Comorbid Conditions
Diabetes
Systemic hypertension
Pulmonary hypertension
Sleep apnea
Obesity/cachexia (body mass)
Renal insufficiency
Hepatic abnormalities
COPD
Clinical Assessment
NYHA functional class (symptoms)
Syncope
Angina pectoris
Systolic vs. diastolic dysfunction
Hemodynamics
LVEF
RVEF
PAP
PCWP
CI
PAP-PCWP
Exercise hemodynamics

Exercise Testing
Metabolic assessment
Blood pressure response
Heart rate response
6-minute walk
Peak Vo_2
Anaerobic threshold
VE/Vco_2
Oxygen uptake slope
Metabolic
Serum sodium
Thyroid dysfunction
Anemia
Acidosis/alkalosis
Chest X-ray
Congestion
Cardiothoracic ratio
ECG
Rhythm (atrial fibrillation or arrhythmias)
Voltage
QRS width
QT interval
Signal-averaged ECG (T wave alternans)
HR variability
Biomarkers
NE, PRA, AVP, aldosterone
ANP, BNP, NT-proBNP, endothelin
TNF, sTNFR 1, sTNFR 2, galectin-3, pentraxin-3, SST2
Cardiac troponins, hematocrit
Endomyocardial Biopsy
Inflammatory states
Degree of fibrosis
Degree of cellular disarray
Infiltrative processes

CI = cardiac width; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; IDCM = idiopathic dilated cardiomyopathy; IL = interleukin; NE = norepinephrine; PAP = pulmonary artery pressure; PAP-PCWP—gradient across lung; PRA = plasma renin activity; PCWP = pulmonary capillary wedge pressure; RVEF = right ventricular ejection fraction; SST2 = somatostatin receptor 2; sTNFR = soluble TNF receptor.
Modified from Young JB: The prognosis of heart failure. In *Mann DL (ed): Heart Failure: A Companion to Braunwald's Heart Disease. Philadelphia, Saunders, 2004, pp 489-506.*

Studies show that Low body-mass index, Broad QRS[22], T-wave alternans[23], Low heart rate variability, Low 6 min walking ability, High left ventricular filling pressure, Restrictive mitral filling pattern[24], Impaired right ventricular function, High serum uric acid [25],high plasma Interleukin –6[26], high plasma Oxidised LDL[27] Low cardiac index, High resting heart rate and High serum norepinephrine[28] portend bad prognosis in these patients. Recently Homocysteine[29]Levels are found to be associated with increased risk of HF.

The inherent limitations associated with these factors necessitate the use of more than one factor in prognostication of chronic HF. Predictability and cost efficacy concerns have inculcated further studies in this area. Recently the prognostic role of T3 in this population is being explored by various studies.

THYROID HORMONE & HEART

The thyroid hormones play a vital role in homeostasis by affecting the hemodynamics of circulation by its multifold effects on the heart and vascular system.[69]

The thyroid hormones metabolically active are Triiodothyronine T3 and Tetraiodothyronine T4.

All of the circulating T4 is produced by the thyroid gland endogenously. T3 on the other hand is mainly obtained from deiodination of T4 in the peripheral tissues. About 20% of T3 is produced directly by the gland.

The cardiac myocytes cannot directly convert T4 to T3 but T3 is the major active form needed for the thyroid hormone mediated effects on the heart.

T3 actions are brought about by acting on certain nuclear receptors thereby regulating the genes encoding for structural and functional cardiac proteins.

Thyroid hormone especially T3 increases cardiac contractility and the heart rate thereby increasing the cardiac output. It also directly and indirectly by increasing peripheral oxygen consumption and substrate requirements.

Triiodothyronine decreases systemic vascular resistance by dilating the resistance arterioles of the peripheral circulation. The vasodilation is due to a direct effect of triiodothyronine on vascular smooth-muscle cells that promotes relaxation. Thyroid hormone increases blood volume. Thyroid hormone also stimulates erythropoietin secretion. The combined

effect of these two actions is an increase in blood volume and preload, which further increases cardiac output[3].

Predictable changes in myocardial contractility and hemodynamics occur across the entire spectrum of thyroid disease. Hyperthyroidism is characterized by increased cardiac contractility, cardiac output and high output failure. Hyperthyroidism induced sustained sinus tachycardia or atrial fibrillation further reduces ventricular contractility[32]. Experimental studies have shown that there is increased expression of beta 1 adrenergic receptors and enhanced catecholamine sensitivity in hyperthyroidism. Hypothyroidism is associated with diastolic hypertension and decreased contractility of myocardium. Hypothyroidism can lead to severe, progressive systolic dysfunction and increased chamber diameter/wall thickness ratio despite a reduction in cardiac mass[33]. There is often pericardial effusion but rarely produces any symptoms.

Subclinical hypothyroidism is diagnosed when serum TSH is high and both T4 and T 3 are normal. Studies indicate that Subclinical hypothyroidism is associated with impaired vasodilatation, which can be corrected with thyroxine therapy[34]. Subclinical hyperthyroidism is diagnosed when serum TSH is low and both T4 and T 3 are normal. There is increased prevalence of atrial fibrillation and increased

cardiovascular mortality[35] in subclinical hyperthyroidism. In contrast Low T3 syndrome is diagnosed when TSH is normal and T3 levels are low.

MECHANISM OF ACTION

Triiodothyronine is the active form that enters the myocyte. In the myocyte, triiodothyronine enters the nucleus and binds to nuclear receptors that then bind to thyroid hormone response elements in target genes and regulates transcription of these genes including those for Ca^{2+}-ATPase[36] and phospholamban[37] in the sarcoplasmic reticulum, myosin, 3-adrenergic receptors, adenylyl cyclase, guanine-nucleotide– binding proteins, Na^{+}/Ca^{2+} exchanger, Na^{+}/K^{+}–ATPase, and voltage-gated potassium channels[u]. In the absence of triiodothyronine, the receptors repress genes that are positively regulated by thyroid hormone. Studies have shown that thyroid hormone can regulate the genetic expression of its own nuclear receptors within the cardiac myocytes.

Thyroxine (T4), which is derived solely from the thyroid gland, normally constitutes the greatest volume of serum thyroid hormone. Triiodothyronine (T3), which is three to five times more potent than T4, is produced both by the thyroid gland and by peripheral conversion of T4 to T3. Conversion involves peripheral monodeiodination of

thyroxine in tissues such as heart, liver, kidney, and gut mucosa by the type I deiodinase. T_3 induces expression of type I deiodinase[38]. The type II deiodinase provides intracellular triiodothyronine in specific sites such as central nervous system and pituitary[39].In addition, T4 is converted to reverse T3 (rT3), a metabolically inactive thyroid hormone, by 5-deiodinase.

LOW T3 SYNDROME

The terms sick euthyroid syndrome, nonthyroidal illness syndrome, euthyroid sick syndrome (ESS) and low T3 syndrome are used interchangeably.

The term low T3 syndrome or sick euthyroid syndrome is defined as "The transient changes in serum thyroid hormone levels as well as the alterations in thyroid hormone metabolism induced by systemic illnesses in patients without concurrent hypothalamic, pituitary or thyroid diseases, and does not imply thyroid hormone status".

This low T3 syndrome had generally been interpreted as an adaptive and beneficial response that decreases the basal metabolic rate. This concept has lately been challenged. Clinical and experimental knowledge of the important role of thyroid hormones especially T3 in cardiovascular homeostasis supports the hypothesis of the direct

relationship between low T3 syndrome and mortality in patients with heart disease.[70]

However more studies are needed about the demonstration of the beneficial effects of long term T3 replacements in cardiac patients (when indicated) before it is brought into practice.

The syndrome has been described in various illnesses like

- Chronic kidney disease[40]
- Tuberculosis, respiratory failure[41]
- Heart failure
- Acute myocardial infarction[42]
- Cardiopulmonary bypass
- Starvation
- Sepsis
- Burns
- Trauma
- Surgery
- Malignancy
- Bone marrow transplantation[43]

The frequency of varies from 20 to 50%. Frequency depends on the severity of illness than on the type of illness. The highest incidence occurs in the most severely ill group.

The syndrome affects both sexes equally and affects people at all ages. Because of the increased incidence of chronic illness at advanced ages the syndrome is more common in elderly age groups.

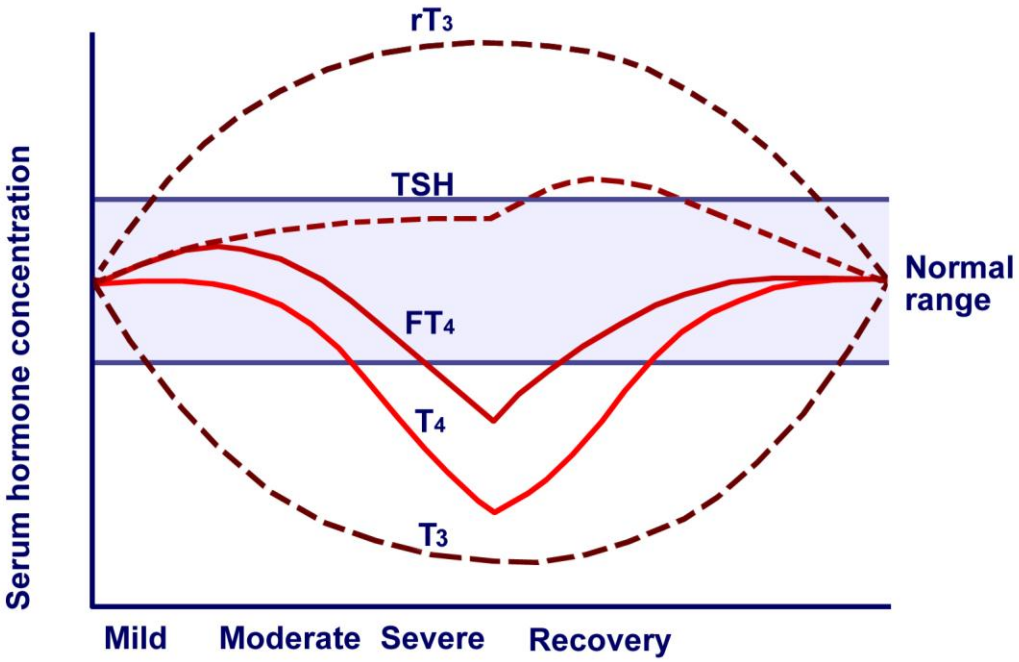
There is no specific imaging study to diagnose low T3 syndrome. Thyroid sonogram, thyroid uptake scan and thyroid biopsy have no role in the diagnosis of this syndrome. There is no typical histological finding in thyroid biopsies.

THYROID PROFILE IN LOW T3 SYNDROME

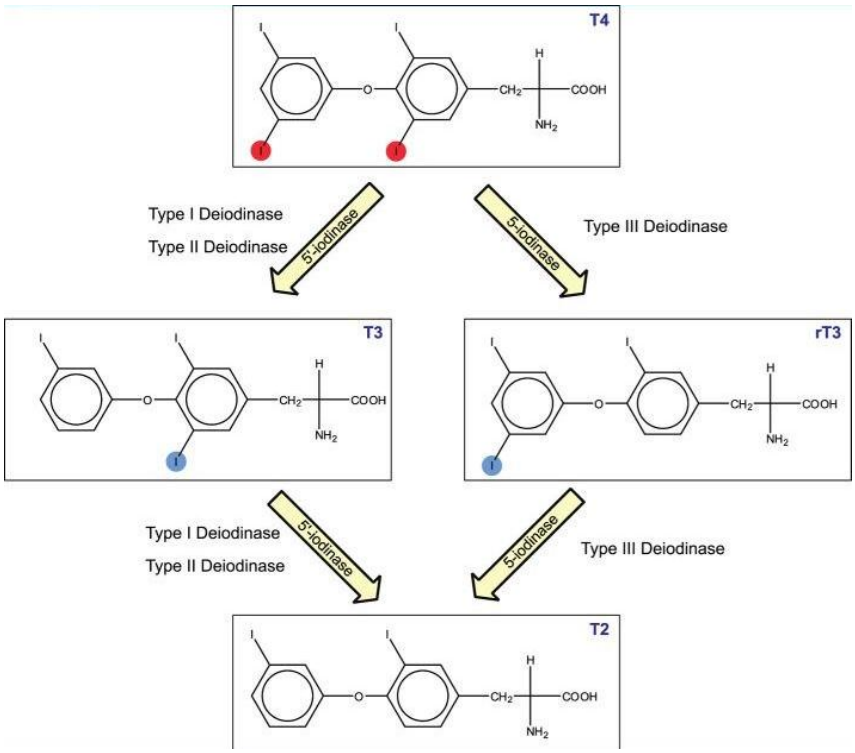
Thyroid hormone estimation is the only test to diagnose low T3 syndrome. The most common[44] hormone pattern in sick euthyroid syndrome is a decrease in total T3 and free unbound T3 levels with normal levels of T4 and TSH. Reverse T3 levels are increased.

As the severity of the sick euthyroid syndrome increases, both serum T3 and T4 levels drop[45] and gradually normalize as the patient recovers. TSH is affected in variable degrees, but, in the overwhelming majority of patients, TSH is in normal range. In severe, critical illness, some patients have reduced T4 levels.

THYROID HORMONES IN LOW T3 SYNDROME



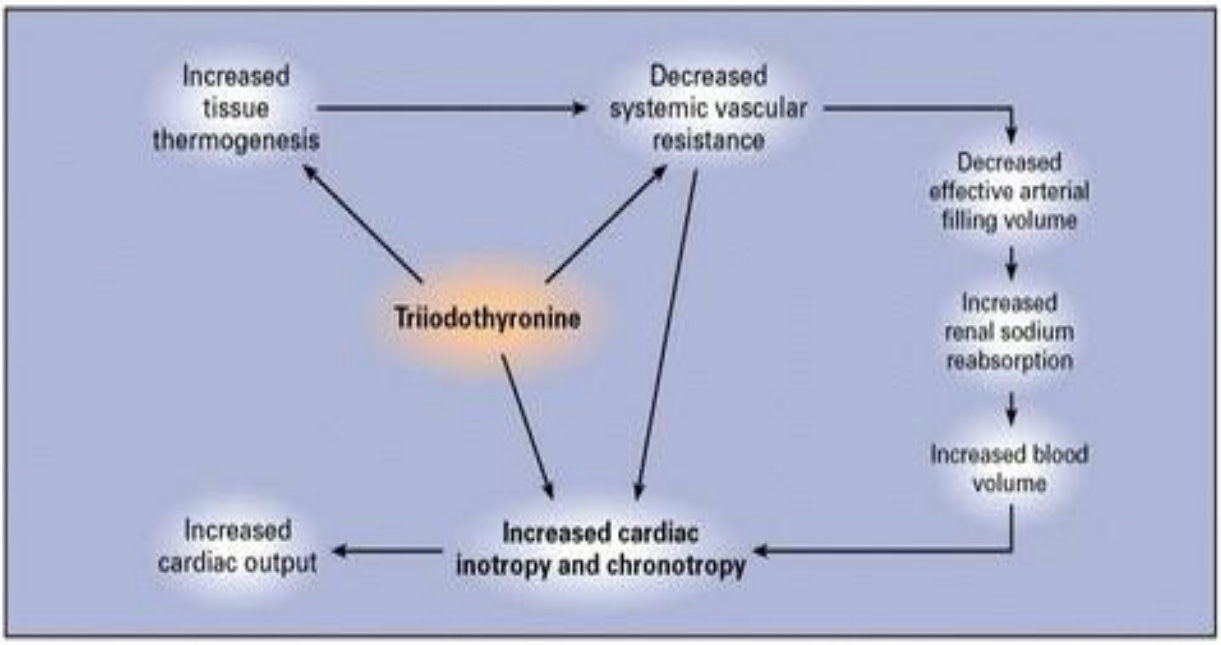
METABOLISM OF THYROID HORMONES



PATHOPHYSIOLOGY OF LOW T3 SYNDROME.

Studies suggest that low T3 levels in heart failure is not just an indication of disease progression but might have an actual pathophysiological role , through interaction with catabolic and inflammatory parameters that have been proven to cause heart failure.

The pathophysiological phenomenon of heart failure involves a multiphasic activation of pro-inflammatory immunological and hormonal systems initially. These initial compensatory mechanisms themselves detrimental eventually becoming maladapted as the disease process evolves. The interaction of T3 with markers like Brain Natriuretic peptide (BNP), adiponectin, etc which are well known prognostic factors in heart failure needs to be probed to understand the intricacies of heart failure better.



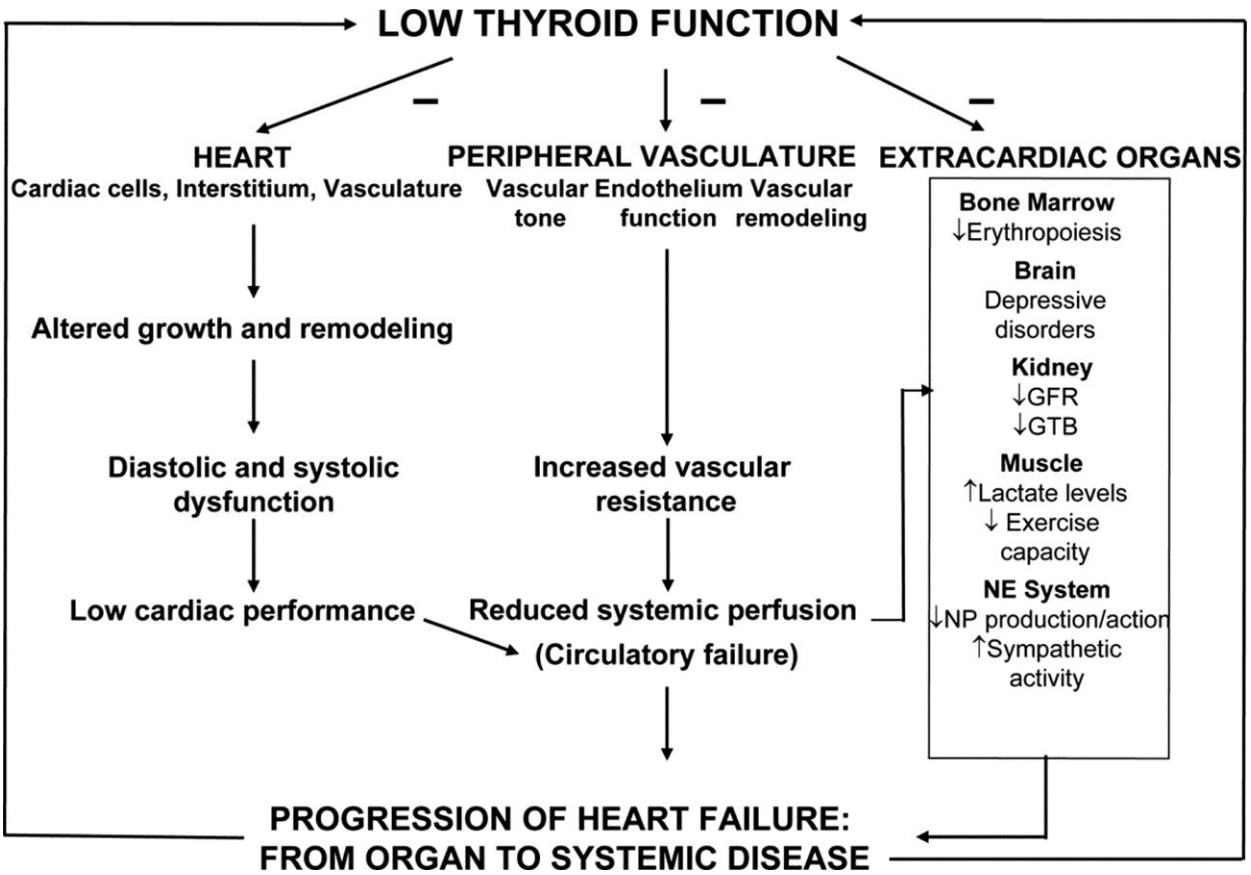
The following mechanisms are implicated in the pathogenesis of low T3 syndrome.

1. Impaired Peripheral deiodination of T4 to T3 secondary to decreased activity of type I deiodinase enzyme, which deiodinates T4 to T3. Normally 20% of T3 production comes from thyroidal secretion and 80% from peripheral deiodination of T4. Though production of T3 by thyroid gland is normal, peripheral production of T3 is decreased. Production of rT3 is unchanged, while its clearance is diminished leading to raised rT3 levels.

2. Increased levels of Cytokines interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha and interferon-beta decrease the activity of type I deiodinase and the binding capacity of T3 nuclear receptors.
3. Presence of binding inhibitor in the serum and in body tissues that might inhibit uptake of thyroid hormones by cells or prevent binding to nuclear T3 receptors, thus inhibiting the action of the hormone.This inhibitor is associated ith the nonesterified fatty acid (NEFA) fraction in the serum.
4. Serum factors, such as bilirubin, NEFA, furanoic acid, hippuric acid, and indoxyl sulphate, present in various non thyroidal illness, have been shown to inhibit transport of thyroid hormones.
5. Diminished T4 has been proposed to be due to low T4 binding globulin caused by protease cleavage at inflammatory sites in acute inflammatory conditions. Another hypothesis for the cause of disproportionately low serum T4 concentrations in

patients with low T3 syndrome is the presence of abnormal serum binding due to desialation of T4 binding globulin.

6. Decreased nocturnal TSH surge ,blunting of TSH response to exogenous TRH and Decreased TRH gene expression[46].
7. The deiodinase enzyme function may be impaired secondary to passive congestion of the liver leading to low free T3 and high reverse T3 levels.



MORTALITY/MORBIDITY IN LOW T3 SYNDROME

Mortality and morbidity depend on the severity and, possibly the duration of the underlying non-thyroid illness. The magnitude of the thyroid function test result abnormalities depend on the severity, rather than the type of illness.

LOW T3 SYNDROME AND CHRONIC HEART FAILURE

The cardiovascular system is one of the most important systems on which the thyroid hormones act.

Theoretically, a low T3 state may give a survival advantage by reducing the energy expenditure of the body and bringing down rates of protein catabolism and help balance the nutritional status overall. But practically however, heart failure symptoms have been shown to worsen because hypothyroidism impairs the intrinsic contractility of the myocardium.

Animal studies show that Cardiac myocyte gene expression and cardiac contractility are reduced in low T3 syndrome and improve significantly with T3 treatment[24.] The LV content of the SERCA2 mRNA is decreased significantly in the low-T_3 syndrome[47]. It is not known whether low-T_3 syndrome is the cause or the effect of chronic heart

failure[48].However majority considered Low T3 syndrome as an adaptive factor in minimizing the catabolic phenomena of heart failure.

Studies indicate that there is a poor relation between measures of cardiac performance and the symptoms of heart failure. Patients with very low ejection fraction may be asymptomatic, where as patients with preserved ejection fraction may develop severe symptoms. This discordance has necessitated research into the role of non-cardiac factors in determining clinical outcomes of heart failure. The existence of these non-cardiac factors may explain why similar pharmacological measures may not produce the same degree of response in all patients. Thyroid hormone due to its fundamental role in cardiovascular homeostasis has been a major area of research in this context. Low T3 syndrome occurs early in chronic heart failure than in other chronic illnesses[49].

The landmark study by Iervasi et al concluded that low T3 concentrations are a strong, independent predictive marker of poor prognosis in heart disease. Studies indicate the prevalence of low T3 syndrome in heart failure between 18 % and 20 %. Recently pingitore et al[50] have shown that alterations in thyroid profile occur in asymptomatic and mildly symptomatic patients with LV dysfunction.

Opasich C et al[51] in a large representative population of moderate to severe heart failure found that sick euthyroid patients have higher NYHA class, weight loss and low insulin levels. Serum norepinephrine levels and atrial natriuretic peptide levels were significantly higher in these patients.

Decreased FT3 levels and FT3/FT4 ratios correlate with reduced ejection fraction and increased chamber dimension[52]..Shimoyama et al, demonstrated lower FT3 values in heart failure patients with ventricular tachycardia[53]. A low free T3 index/reverse T3 ratio was associated with higher right atrial, pulmonary artery and pulmonary capillary wedge pressures and lower ejection fraction, cardiac index, serum sodium, albumin and total lymphocyte count[54.] It is not known whether sick euthyroid syndrome contributes to the development of heart failure or is only an attendant syndrome.

Brenta et al[71], in their study published in the European journal of endocrinology studied the association of low T3 levels with important hemodynamic, metabolic and neurohormonal parameters which are also significant prognosticators in congestive heart failure. They concluded that lower T3 levels correlated with higher hsCRP, adiponectin and NT-proBNP levels and with lower adrenal steroid DHEAS, with lower BIA (

bioelectrical impedance analysis) phase angles that evaluate body composition and are markers of membrane damage at the cellular level.

A low free t3/reverse T3 ratio is associated with poor ventricular function.

LOW T3 SYNDROME THERAPEUTIC ASPECTS

Limited numbers of studies have determined the effects of thyroid hormone supplementation in low T3 syndrome. In 23 patients with advanced heart failure Hamilton et al found a single intravenous dose of 58 µg of triiodothyronine resulted in an increase in cardiac output and a decrease in systemic vascular resistance two hours after administration, without any evidence of myocardial ischemia, rhythm disturbances, or other untoward effects. High dose of triiodothyronine decreased systemic vascular resistance and increased cardiac output within hours after coronary artery bypass grafting[55].

A randomised placebo control trial that supplemented oral levothyroxine 100 micrograms in patients with heart failure due to ischemic cardiomyopathy but normal thyroid function tests and found improvement in cardiac performance in the form of improved inotropy, increase in cardiac output, functional capacity and reduced systemic vascular resistance.[71]

Moruzzi et al[56], in a placebo controlled study of 20 patients with chronic heart failure found that treatment with 0.1 mg of thyroxine daily for 12 weeks improved exercise performance, increased the cardiac index, and decreased systemic vascular resistance.

Psirropoulos, D et al have found exercise training, through a wide variety of mechanisms, can normalise free triiodothyronine levels reverses sick euthyroid syndrome in heart failure[57].

3,5 doiodothyropropionic acid (DITPA) is a thyroid hormone analogue with relative selectivity for a form of the thyroid hormone receptor in the liver. DITPA improves systolic as well as diastolic function[58] and is presently under trials.

Whether thyroid hormones should be used in all patients with low T3 syndrome remains controversial due to lack of large scale controlled trials. Safety and hemodynamic benefits of longer infusions, combined infusion with inotropic agents, oral triiodothyronine replacement therapy, and new triiodothyronine analogues have to be studied in future.

In a study by Rothberger et al, 137 patients without thyroid disease or treatment with drugs which affect TH levels, who were hospitalized with acute HF were prospectively enrolled and studied. TH levels were tested upon hospital admission, and outcomes were compared between

patients with low (<2.3 pg/ml) and normal (≥2.3 pg/ml) free T levels as well as between those with low (<0.6 ng/ml) and normal (≥0.6 ng/ml) total T levels. Low free T correlated with an increased length of stay in the hospital and higher rates of intensive care unit admission with a trend toward increased need for invasive mechanical ventilation.[73]

MATERIALS AND METHODOLOGY

MATERIALS AND METHODOLOGY

STUDY DESIGN

Prospective study

SETTING

All patients were prospectively enrolled from the Cardiology and Internal medicine department of Government General Hospital, chennai.3.

SAMPLE

100 patients with clinical evidence of heart failure were enrolled in this study after applying inclusion and exclusion criteria. All patients had documented evidence of prior myocardial infarction and were on heart failure treatment for at least one month. Informed consent was obtained from all patients.

INCLUSION CRITERIA

1. Duration of heart failure for a minimum period of one month
2. Left ventricle ejection fraction less than 40%

EXCLUSION CRITERIA

1. History or clinical or laboratory evidence of hypothyroidism
2. History or clinical or laboratory evidence of hyperthyroidism

3. Subclinical hypothyroidism and Subclinical hyperthyroidism
4. Amiodarone therapy
5. History of revascularisation procedures
6. Clinical evidence of Sepsis
7. Evidence of renal failure
8. Any other severe systemic illness

PROCEDURE

A questionnaire prepared noted the duration, symptoms and treatment of heart failure. Questions were asked in relation to chest pain, dyspnoea, syncope, cough, smoking and medications. All previous clinical records of the patients were analysed in detail. Based on the degree of effort needed to elicit symptoms patients were assigned to NYHA (New York Heart Association) class I to IV.

A detailed physical examination was conducted to assess patients' volume status (rales, edema, jugular venous distension), weight, height, body mass index and orthostatic blood pressure changes.

Complete blood count, blood glucose, fasting serum lipid profile, blood urea, serum creatinine and serum electrolytes were measured in all patients.

Two-dimensional echocardiography was done in the cardiology department of Government General Hospital all patients.

Thyroid hormone measurements TSH, total T3, total T4, free T3, free T4 were done in all patients.

INSTRUMENTS

1. ELECTROCARDIOGRAM:

All patients had 12 lead ECG, which was reviewed for evidence of atrial enlargement, ventricular hypertrophy, evidence of antecedent myocardial infarction and conduction blocks

2.CHEST X RAY:

Chest x ray posteroanterior view was done in all patients to note pulmonary congestion, pleural effusion and to estimate cardio thoracic ratio.

3. ECHOCARDIOGRAPHY:

M-mode echocardiography was used to assess left ventricle dimensions. Left ventricle internal dimension in end systole (LVESD) and end diastole (LVEDD) are measured at the level of mitral valve leaflet tips in parasternal long axis view. Measurements are taken from the endocardium of the left surface of the interventricular septum to the endocardium of the left ventricle posterior wall. In adults the normal

range of LVEDD is 3.5 to 5.6 centimeter. The normal range of LVESD is 2 to 4 centimeter[59].

2-D echo imaging in apical 4 chamber, parasternal long axis and parasternal short axis views were used to assess ventricular and valvular movement. Ejection fraction was estimated using Simpson's method[60]. In this method multiple short axis views are taken along the LV long axis. Endocardial border is traced accurately and left ventricle cavity is divided into 20 slices of known thickness and diameter (D). Left ventricle end diastole and Left ventricle end systole volumes are estimated.

Area of each slice=22/7 $(D/2)^2$

Volume of each slice = area X thickness.

LV volume= volume of each slice X number of slices (20)

$$EF(\%) = \frac{V_{ed} - V_{es}}{V_{ed}} \times 100$$

V_{ed} - End diastolic Volume

V_{es} - End systolic Volume

LABORATORY METHODS

Fasting plasma glucose was measured using glucose oxidase and pyruvate oxidase methods from overnight fasting sample and results were read by autoanalyser.2 hr postprandial glucose was measured 2 hrs after routine morning breakfast.

From patients height and weight body mass index (BMI) was calculated using the formula weight in kilograms divided by square of height in meters. Serum cholesterol (enzymatic oxidase-peroxidase method), Serum HDL (polyethylene glycol-CHOD-PAP method) Triglycerides (enzymatic calorimetric method) were measured using Erba XL 300 autoanalyser. Serum LDL was calculated using Friedewald's formula[61].

LDL-C = Total cholesterol-TGL/5 If TC less than 400 mg/dl. TSH, Total T3, Free T3, Total T4 and Free T4 were measured by chemiluminescent immuno assay (CLIA) method. The normal values of our laboratory were

TSH: 0.35 to 4 mIu/L,

Total T3: 80 to 200 ng/dl,

Free T3: 2.3-4.2 pg/ml,

Total T4: 4.5-12 microgram/dl, and Free T4 7.5 to 18 pg/ml.

DEFINITIONS:

1. **Newyork Heart Association classification of heart failure[62]**

   Class I No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea, or palpitations

   Class II Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitation or dyspnoea

   Class III Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms.

   Class IV Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity

2. **DYSLIPIDEMIA[63]**

   Any one of

   - Serum total cholesterol >/= 240 mg/dl
   - Serum HDL </= 40 mg/dl
   - Serum triglycerides >/= 200 mg/dl
   - Serum LDL >/= 160 mg/dl

3. **DIABETES MELLITUS[64]**

   1. Plasma glucose of 126mg/dl or greater after overnight fasting
   2. Post prandial Plasma glucose of 200 mg/dl or greater

3. Symptoms of DM with random glucose 200 mg/dl or greater

4. SYSTEMIC HYPERTENSION

Based on JNC 8[65] classification systolic BP of 140 mm Hg and above and diastolic BP of 90 mm Hg and above was defined as systemic hypertension.

5.OBESITY

Obesity is defined as body mass index more than 30 $kg/m^{2.}$

FOLLOW UP

Follow up of 100 patients began when thyroid hormone levels were measured. 24 patients were lost during follow up period.

25 patients died during the follow up period of 6 months. Of the 25 patients, 15 patients died due to progressive heart failure/shock, arrythmia, cardiac arrest or myocardial infarction. 3 patients had sudden death outside hospital. The cause of death in the other 7 patients could not be ascertained as some did not seek medical attention or hospital records during the time of death could not be obtained. 51 patients survived the 6 month period. 24 patients were lost during the follow up period. At the end of the follow up period characteristics of the all-cause mortality of the died group and the survived group were compared and analysed.

STATISTICAL ANALYSIS

Statistical analysis was carried out for the 76 subjects (51 alive, 25 died). Age, sex, BMI, diabetes, hypertension, dyslipidemia, obesity, smoking, left ventricle end diastolic diameter, NYHA class, Ejection fraction, TSH, Total T3, Free T3, Total T4 and Free T4 were analysed. Results were expressed as Mean and Standard Deviation(SD). The significance of difference in means between two groups was calculated using student t test and the significance of difference in proportions using chi-square statistic. Statistical significance was taken when $p<0.05$.All variables with significant associations were entered in Cox proportional Hazard Model for multivariate analysis with 95% confidence intervals. Pearsons correlation was used to analyse correlation between variables that were found to be significant in multivariate analysis. All statistical analyses were performed using SPSS (statistical package for social sciences) software for windows.

RESULTS

RESULTS

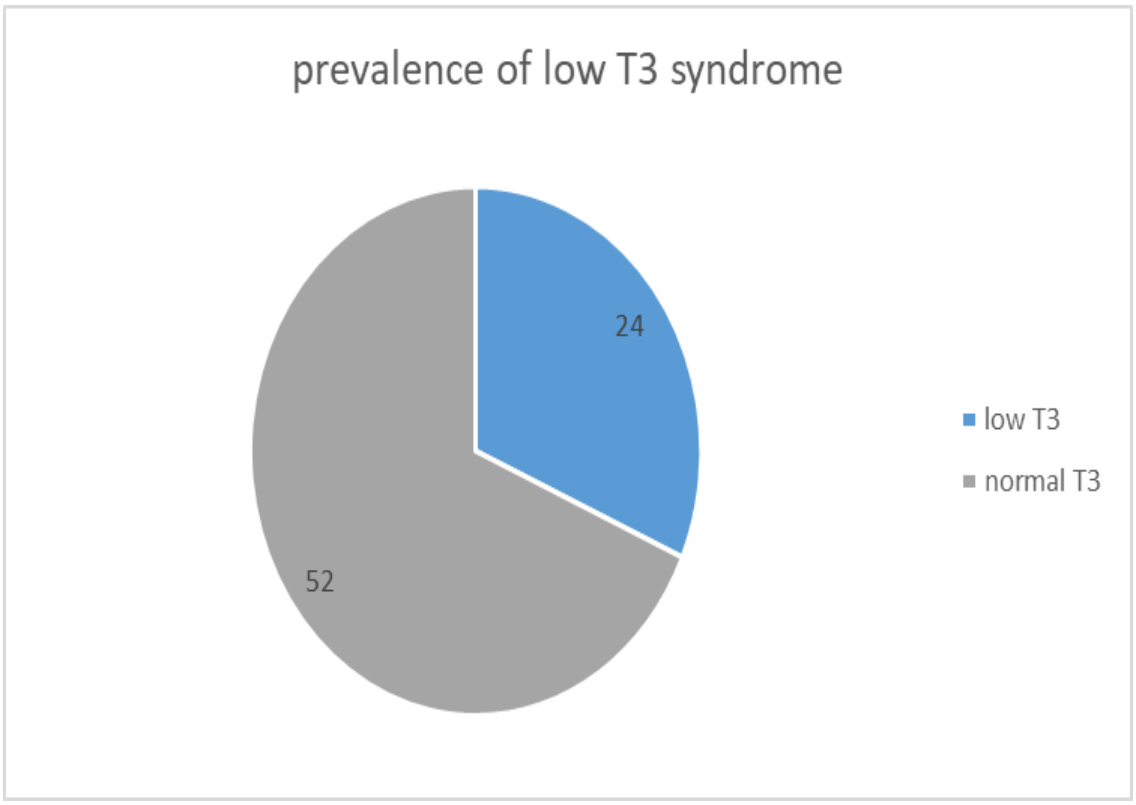
Table 1

Prevalence of low T3 levels

Total T3	N= 76	Percent with low T3
T3< 80	24	31.57
T3>/=80	52	

Total T3 values of all the 76 patients were computed.24 of the 76 patients had Total T3 less than the lower limit of 80 ng/dl. The prevalence of low T3 I s found to be 31.57%.

Comparison of continuous variables age, BMI, NYHA class, EF, LVEDD and thyroid profile values was done with student t test. The mean age of patients in died group was 65.96 and 58.23 in the survived group.



PREVALENCE OF LOW T3 SYNDROME- 31.57%

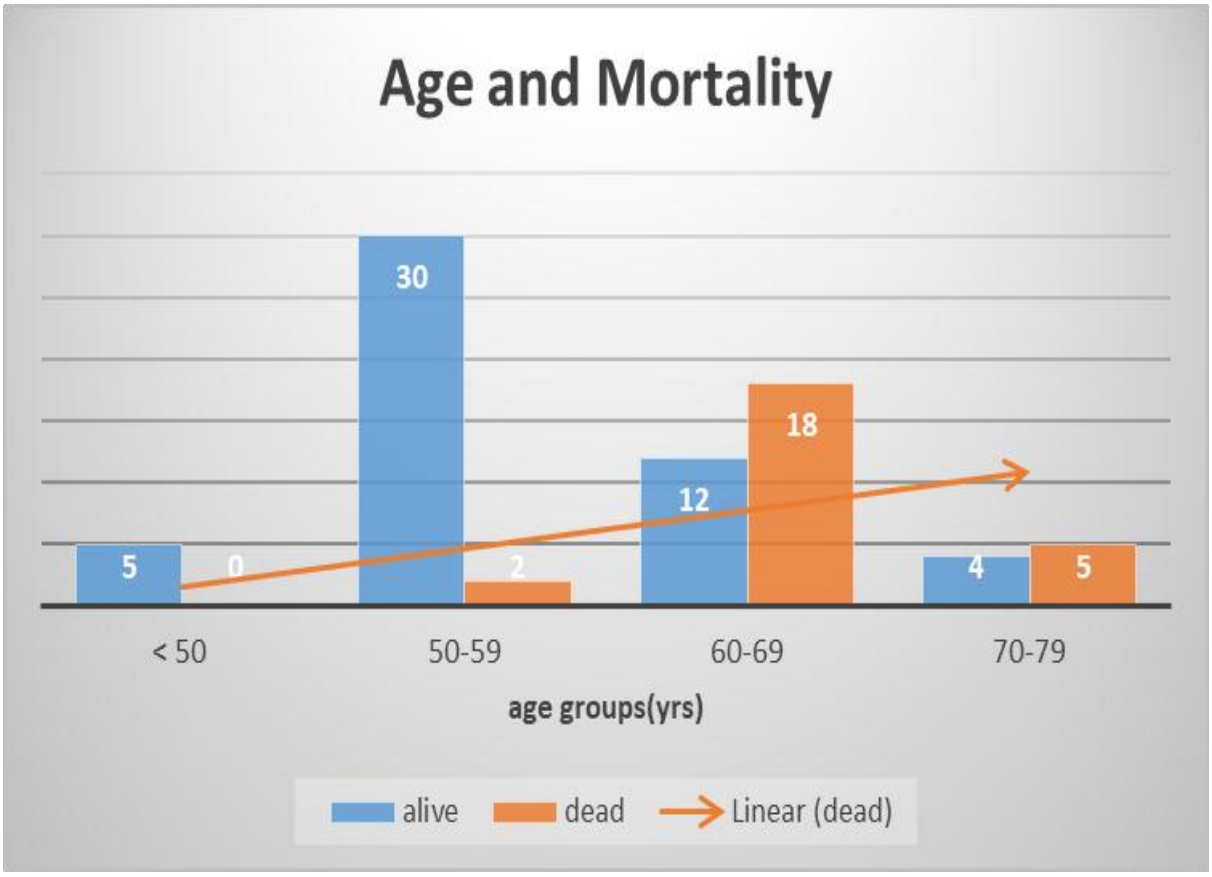
Table 2

Comparison of Age, BMI and NYHA class

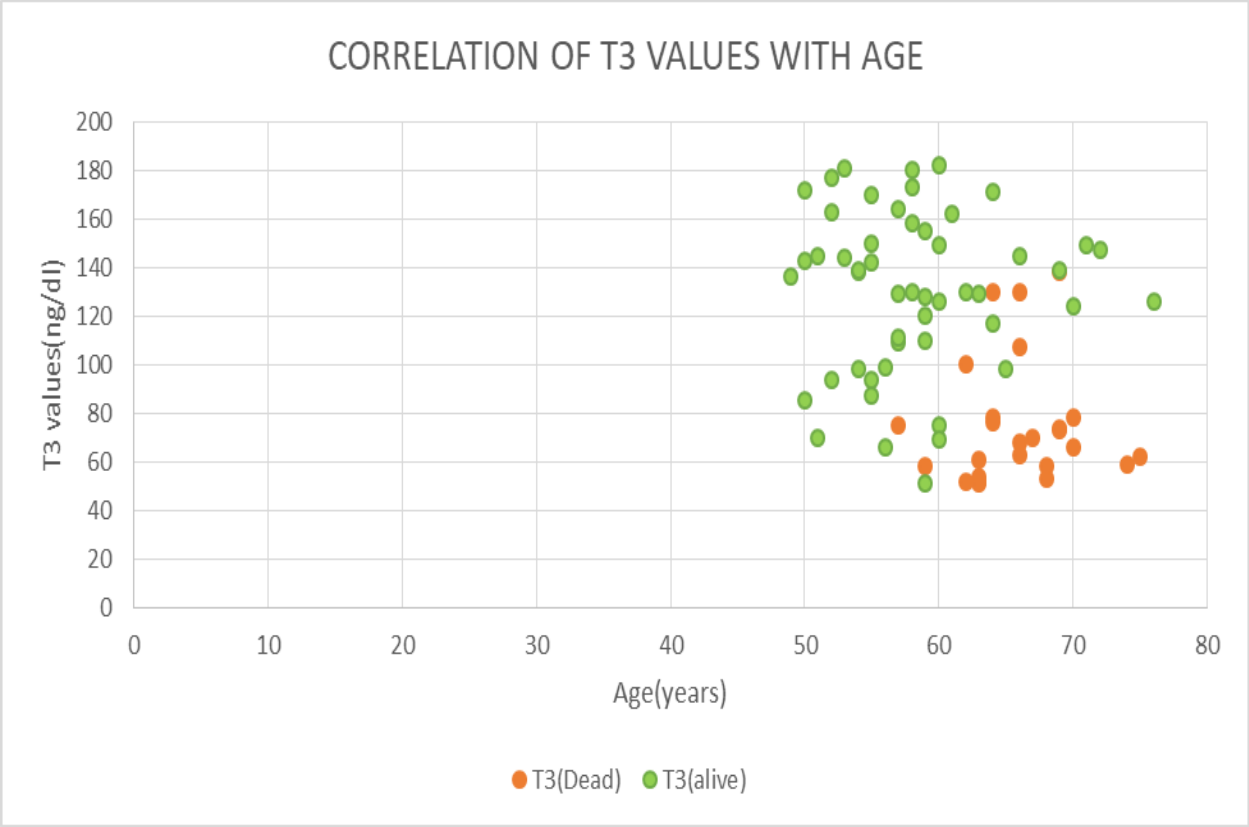
variable	Group	Number	Mean P	SD	P value Student t test
Age	Died	25	65.96	4.18	0.001 Significant
	Alive	51	58.23	6.07	
BMI	Died	25	26.87	2.86	0.43 Not Significant
	Alive	51	27.44	3.04	
NYHA Class	Died	25	3.32	0.8	0.02 Significant
	Alive	51	2.8	0.98	

P value less than 0.05 is considered statistically significant. Values are rounded up to two decimals.

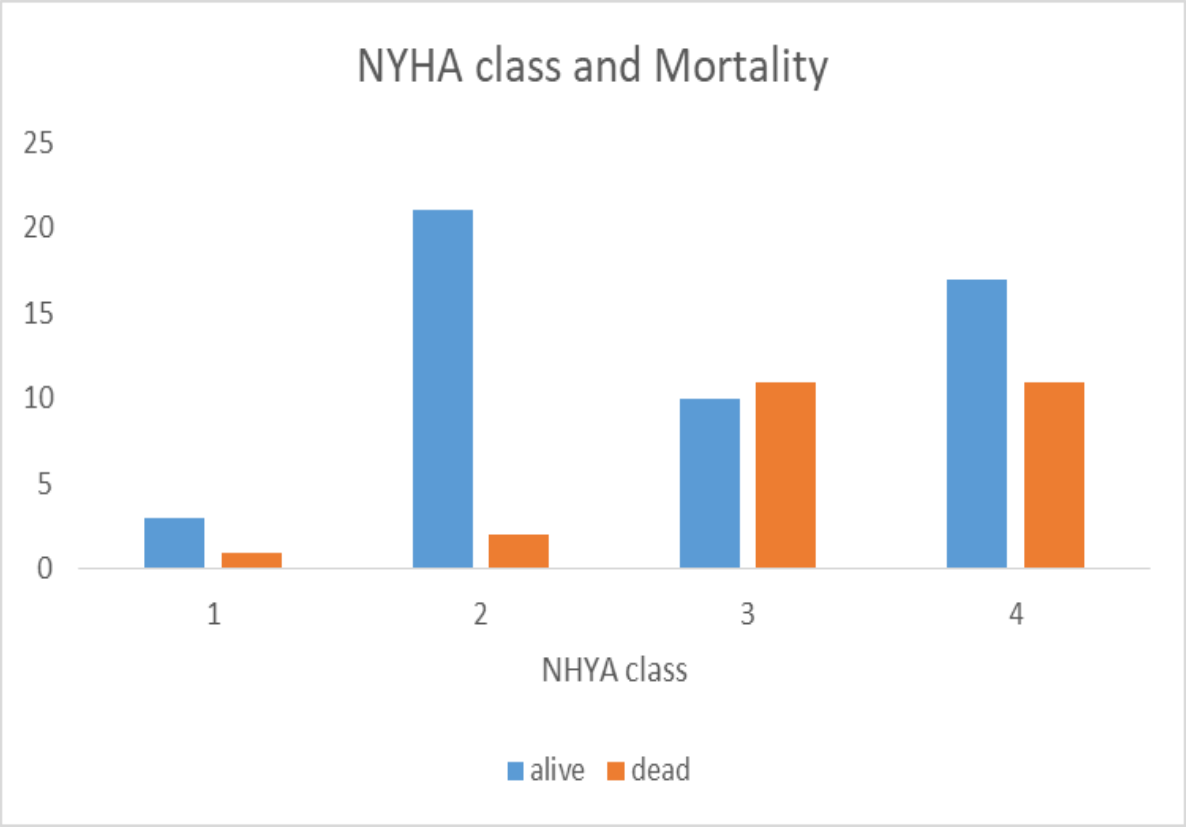
SD denotes standard deviation.



There was a statistically significant association between increasing age and mortality independent of other factors.The trend line shows a linear association between age and mortality.



This scatter plot shows that mean T3 values were lower in the deceased patients than in the patients on followup.



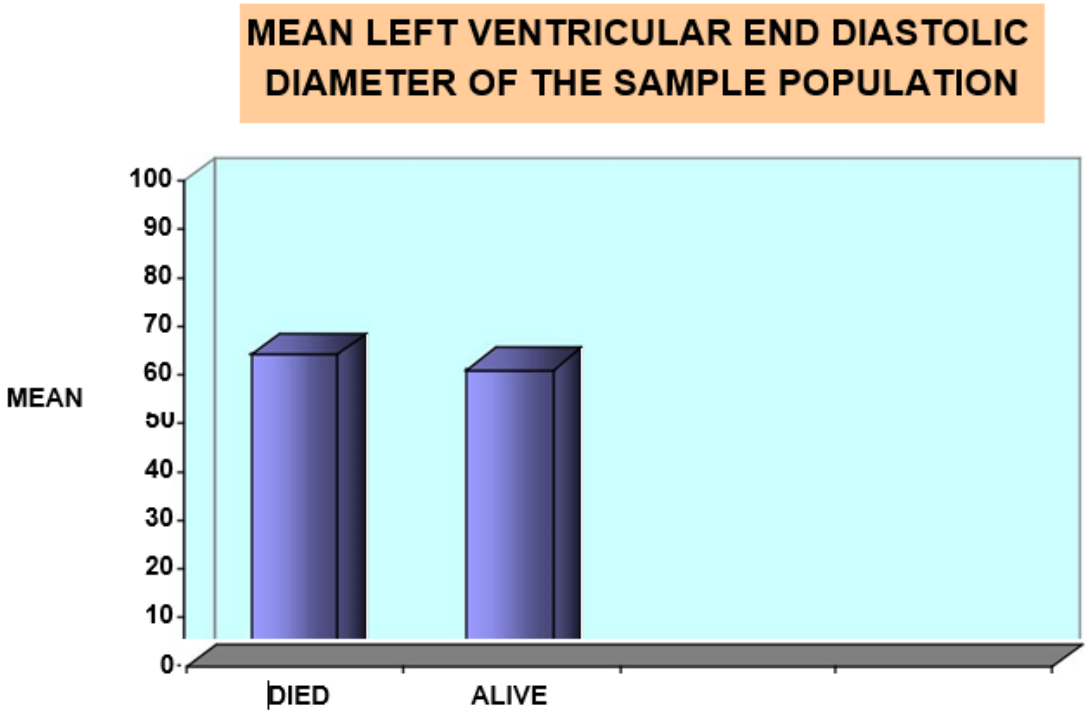
There is significant difference in age and NYHA class between the two groups. The mean age was higher in the died group and these patients were in worse NYHA class.

Table 3

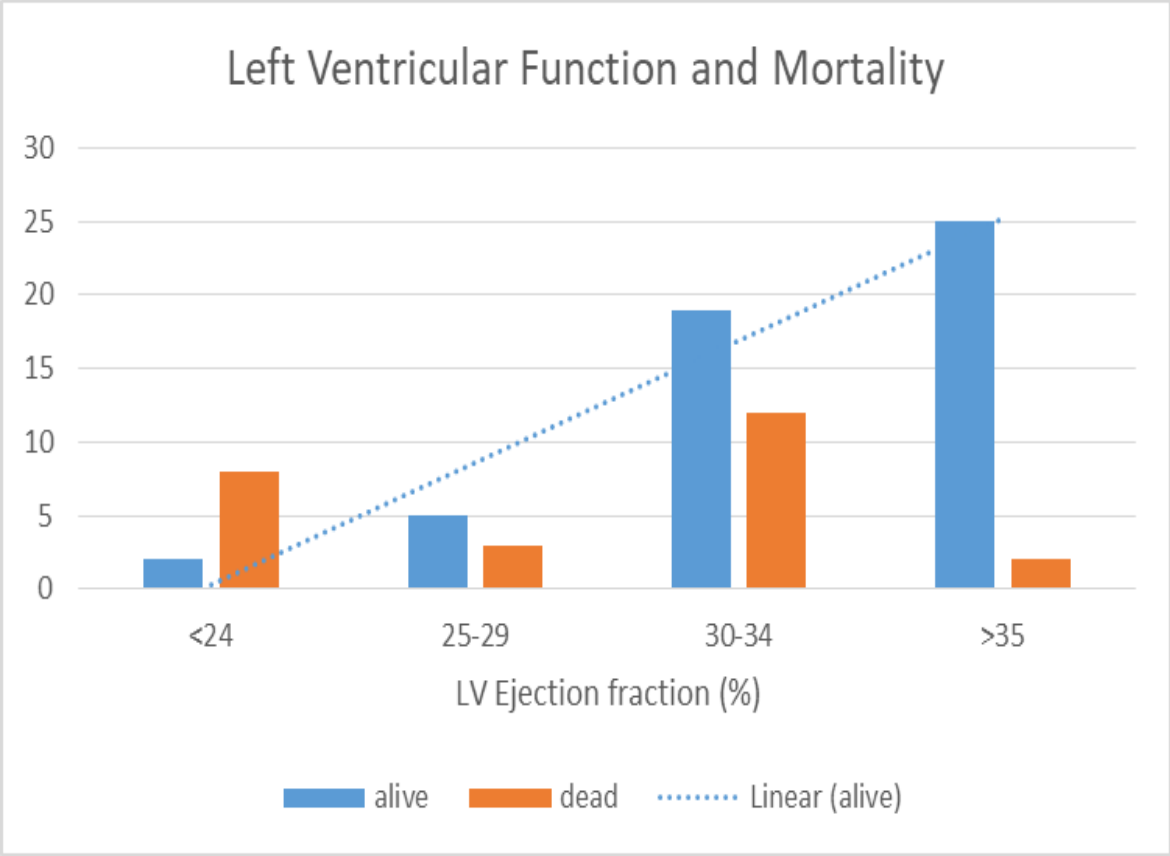
Analysis of Echocardiographic parameters

Variable	Group	N	Mean	SD	P value Student t test
Ejection Fraction	Died	25	28.36	6.75	0.001 Significant
	Alive	51	34.88	5.45	
LVEDD	Died	25	64.04	5.26	0.001 Significant
	Alive	51	60.84	3.49	

Compared to patients who are alive, left ventricular end diastolic diameter was higher in those who died. The mean ejection fraction in died and alive groups were 28.36 and 34.88 respectively.



Persons who died had a significantly lower ejection fraction than those alive. When the mean ejection fraction was compared between patients with low total T3(T3<80 ng/dl) and normal T3, patients with low T3 had a mean ejection fraction of 29.2 and those with normal T3 levels had a mean ejection fraction of 34.78. This indicates mean ejection fraction is lower in patients with low total T3 levels.

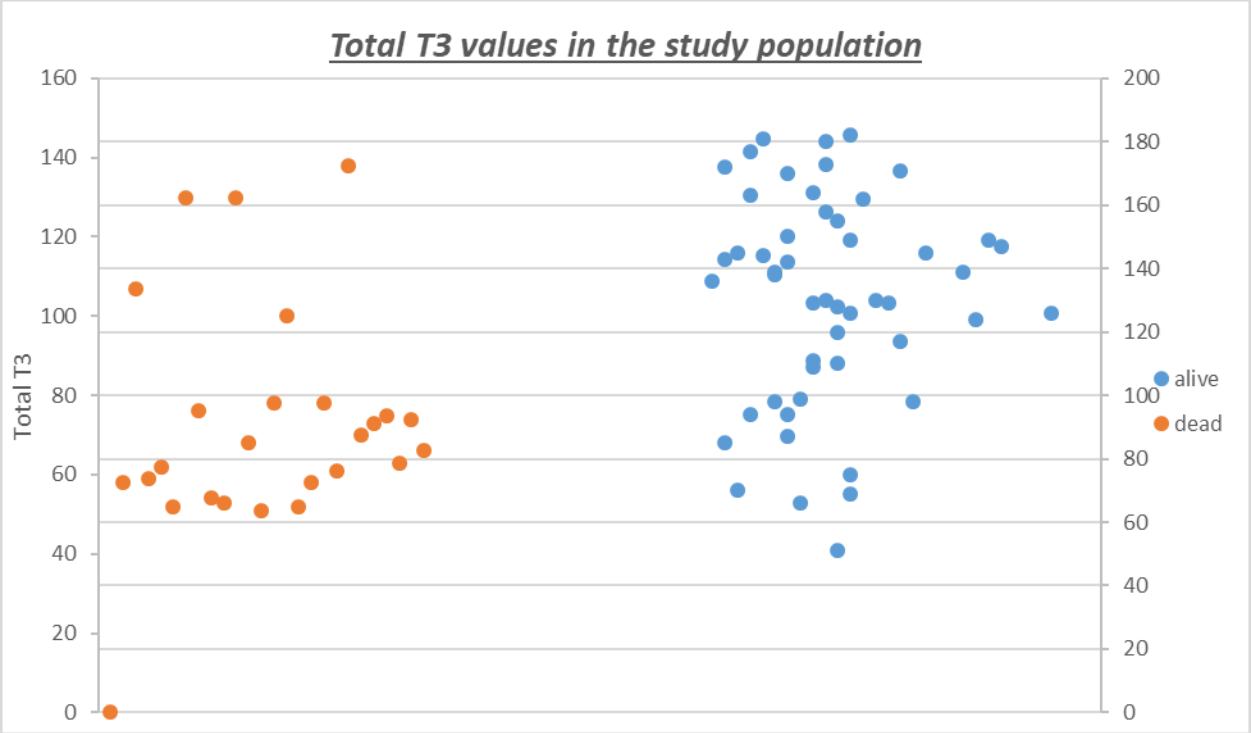


The trend line shows a linear correlation between declining Left ventricular systolic unction and mortality.

Table 4

Analysis of TSH, Total T3, Free T3 levels

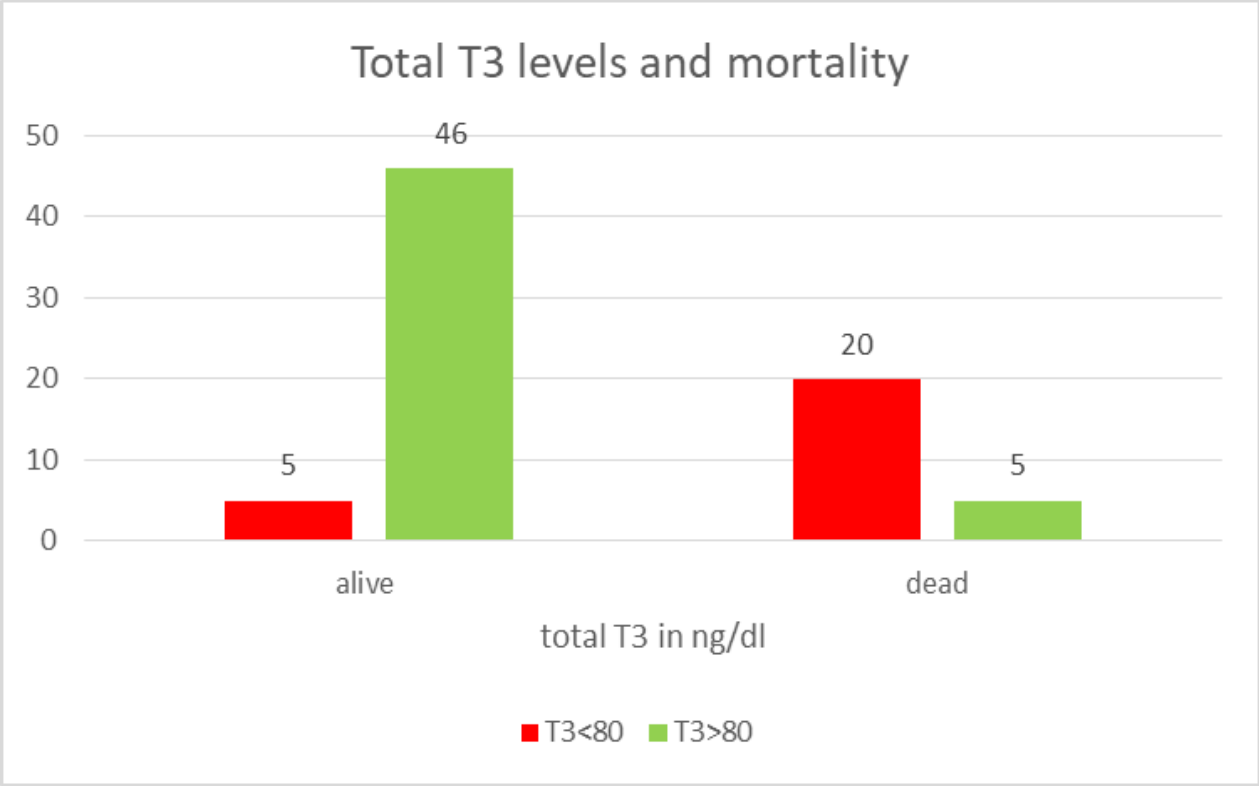
	Group	N	MEAN	SD	Student t test
TSH	Died	25	2.81	0.83	P=0.51
	Alive	51	2.68	0.86	NS
Total T3	Died	25	75.09	25.64	P=0.001
	Alive	51	130.23	33.39	Significant
FreeT3	Died	25	2.04	0.85	P=0.001
	Alive	51	3.35	0.67	Significant



This scatter diagram shows the distribution of Total T3 values (ng/dl) of our study population. The distribution shows a trend towards lower T3 values among the deceased population compared to the patients on follow up.

The mean Total T3 values were 75.09 ng/dl (dead) and 130.23 ng/dl (alive).

The association between low T3 and mortality was statistically significant.(P=0.001)



In alive group 9.8% had low total T3 levels (< 80 ng/dl) as against 80% in those who died. The mean total T3 and free T3 levels were significantly less in died patients.

Table 5

Analysis of Total T4, Free T4 levels

	Group	N	MEAN	SD	Student t test
Total T4	Died	25	7.21	1.52	P=0.07 Not Significant
	Alive	51	7.97	1.83	
Free T4	Died	25	13.76	2.67	P=0.26 Not Significant
	Alive	51	14.47	2.53	

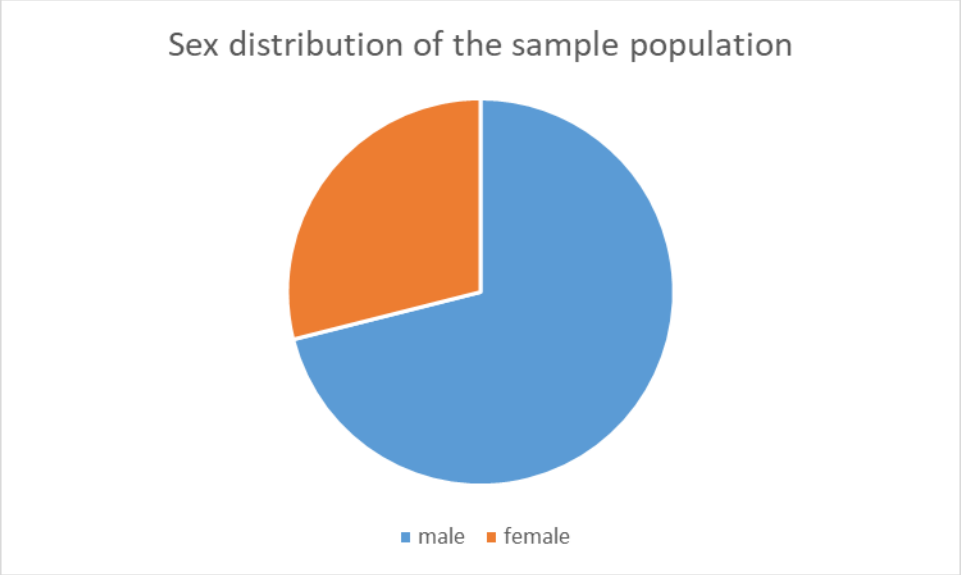
Mean total T4 was less in those who died but there was no statistical significance between the two groups in total T4 and Free T4 levels.

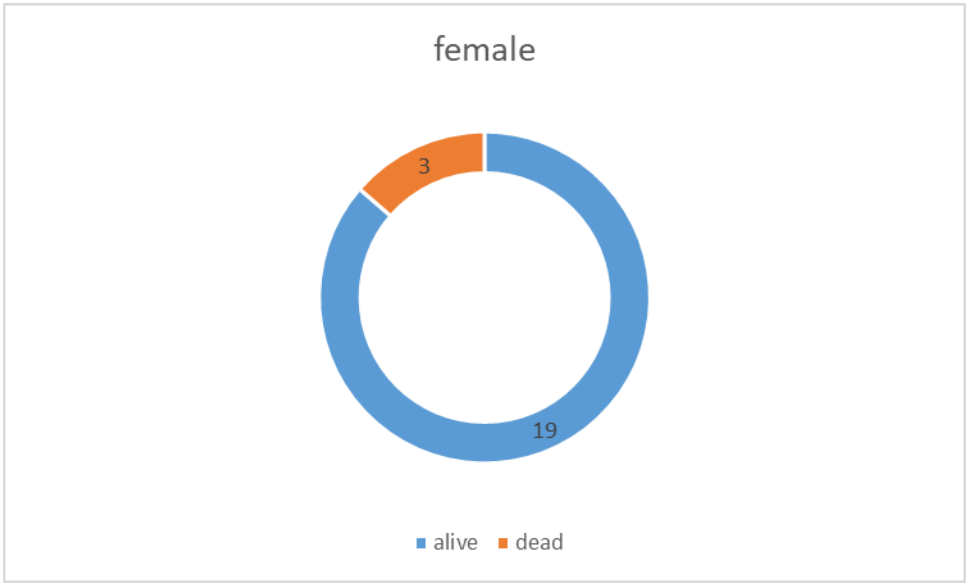
Dichotomized variables sex, hypertension, obesity, diabetes, dyslipidemia, smoking were analysed using chi-square test.

Table 6

Analysis of Sex characteristics

Variable		Alive		Died		Test value
		N	%	N	%	Chi-square Test
Sex	Male	32	62.7	22	88	$\chi 2=4.57$
	Female	19	37.3	3	12	P=0.03 Significant

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3
19
alive
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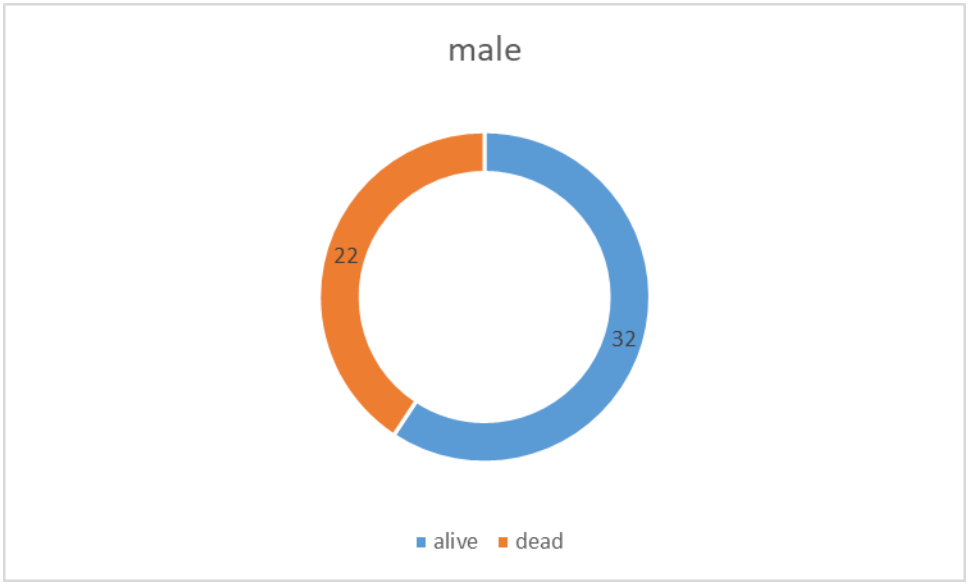
male
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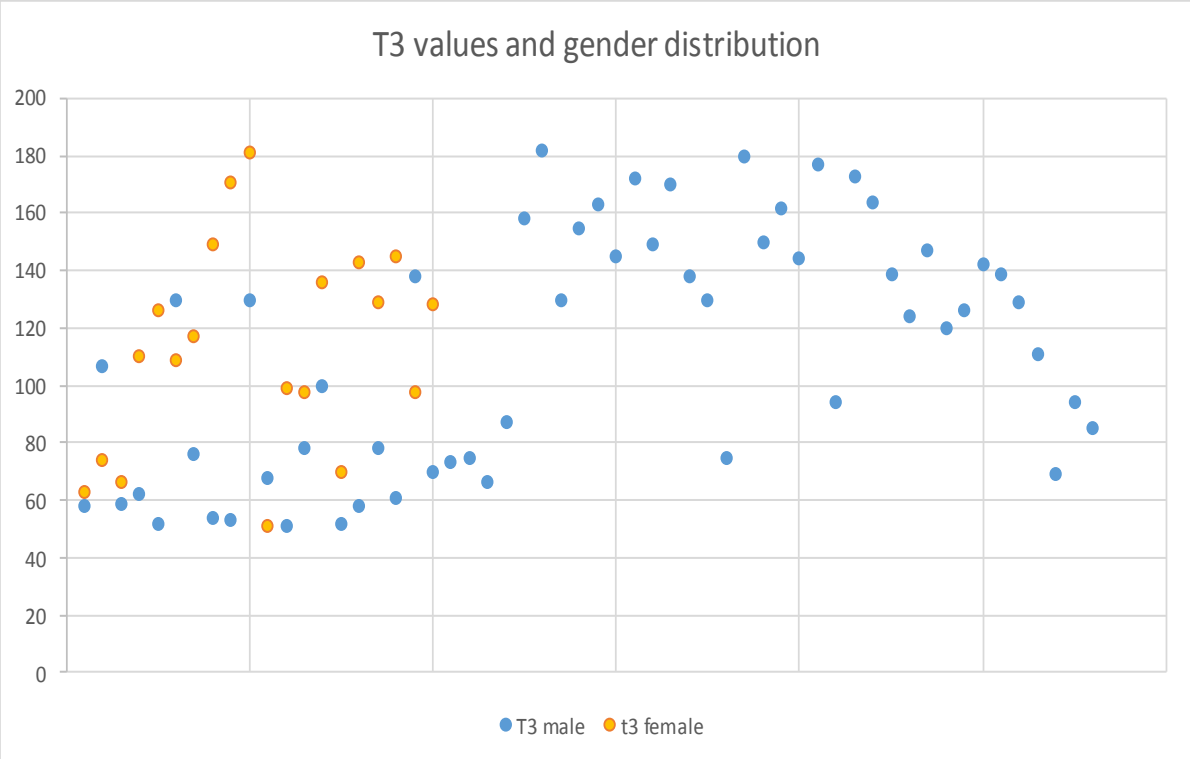
alive
dead



22 (28.94%) of the 76 analysed were females. Males accounted for 88% of those who died. There exists a statistically significant difference in mortality between male and female sex.

Table 7

Analysis of BMI, Diabetes, Hypertension

Variable			Alive	Dead		Test value
	N		%	N	%	Chi-square test
BMI	<25	16	31.4	6	24	$\chi 2$=0.44
	>/=25	35	68.6	19	76	P=0.51 NS
DM	NO	32	62.7	15	60	$\chi 2$=0.05
	YES	19	32.3	10	40	P=0.81 NS
SHT	NO	26	51	15	60	$\chi 2$=0.55
	YES	25	49	10	40	P=0.45 NS

NS- Not Significant

Presence of diabetes, systemic hypertension or BMI>/= 25 were not significantly different in those who died, compared to those who survived.

Table 8

Analysis of Dyslipidemia, Obesity,B-blocker use, smoking

Variable			Alive	Dead		Test value
		N	%	N	%	Chi-square test
Dyslipidemia	NO	27	53	16	64	$\chi 2$=0.84
	YES	24	47	9	36	P=0.36 NS
Obesity	NO	33	64.7	20	80	$\chi 2$=1.86
	YES	18	35.3	5	20	P=0.17 NS
B-blocker Use	NO	20	39.2	11	44	$\chi 2$=0.16
	YES	31	60	14	56	P=0.69 NS
Smoking	NO	25	49	12	48	$\chi 2$=0.01
	YES	26	51	13	52	P=0.091NS

NS- Not Significant

Dyslipedemia,Obesity,Beta blocker use and smoking did not influence mortality significantly.

From the above analysis Age, sex, NYHA class, ejection fraction, LVEDD, Total T3and Free T3 were significantly altered in died patients. To assess the influence of these parameters on mortality multivariate analysis was done. Because total T3 and free T3 are highly correlated we did not include free T3 in the same proportional hazard model.

Table 9

Cox proportional Hazard Model for Heart failure mortality

Variable	Significance	Odds ratio	95% CI	
			Lower	Upper
Age	.001	45.453	5.420	381.145
Sex	.045	.260	.070	.968
LVEDD	.636	.784	.286	2.148
EF	.041	2.455	1.025	6.967
Total T3	.001	19.05	4.65	111.1
NYHA	.118	1.564	.892	2.741

Age, sex, EF (ejection fraction) and total T3 were significant. Association between these variables was evaluated by Pearson product moment correlation test.

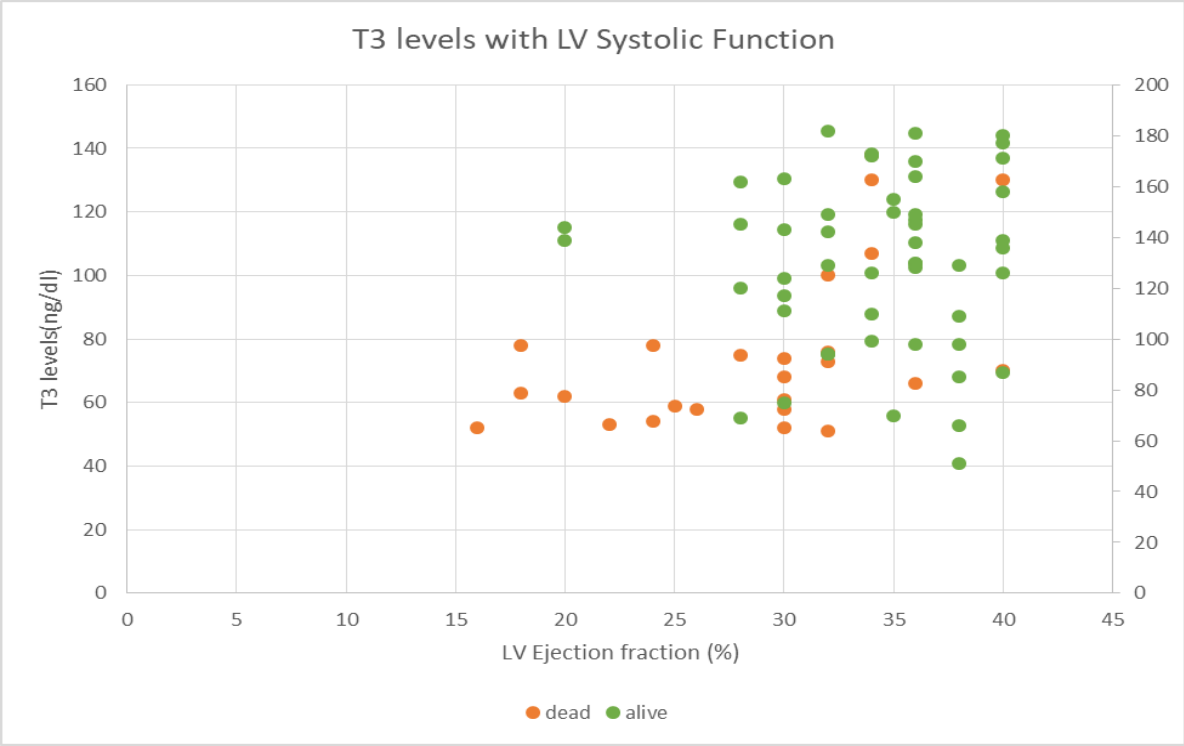
Table 10

Association of total T3 with EF, Age, Sex

Variable		**EF**	**Age**	**Sex**
	Pearson Correlation. r (2 tailed)	0.405	-0.346	0.054
Total T3	Significance	<0.001 Significant	0.002 Significant	0.641 NS
	N	76	76	76

NS- Not Significant

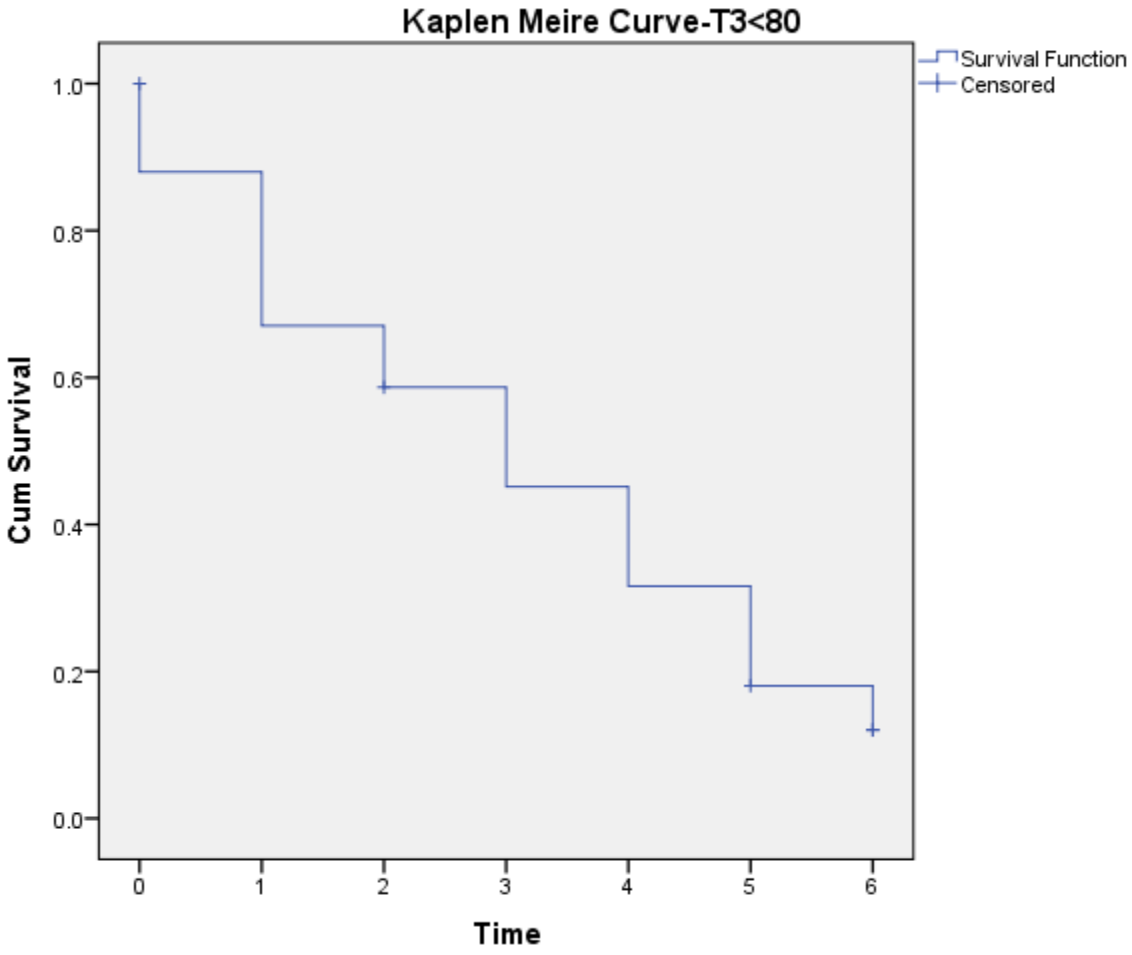
Correlation is significant at 0.01 level (2-tailed).

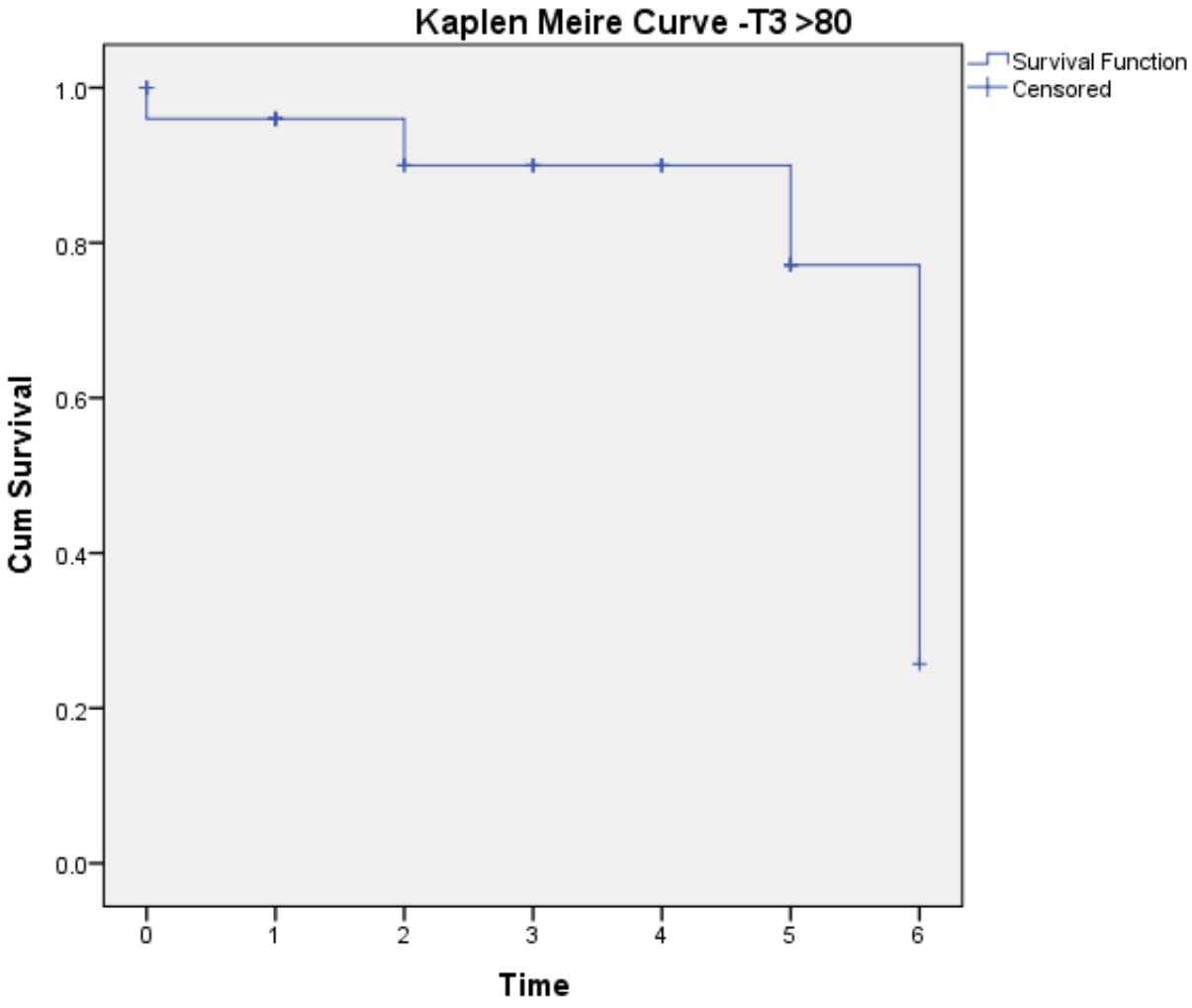


The results show a significant correlation of total T3 with ejection fraction, indicating patients who have low ejection fraction have low total T3 levels. Total T3 levels did not correlate with sex. There is significant correlation between advancing age and lower total T3 levels.

Using a cut-off total T3 level of 80 ng/dl (the lower limit of normal) two subgroups were identified and Kaplan-Meier survival analysis was compiled. Survival at 6 months in low total T3 group was found to be less than the group with total T3 80 ng/dl and above.

Kaplan-Meier 6-month survival curves for all cause mortality in two sub groups identified according to total T3 cut off value of 80 ng/dl.




Kaplen Meire Curve -T3 >80
Survival Function
Censored
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Time

DISCUSSION

DISCUSSION

In this study of Indian population involving 76 patients, we evaluated the prevalence of low T3 syndrome in chronic heart failure. We found the prevalence of low T3 syndrome to be 31.57%. This is similar to one study but higher than those described in other studies. Studies by Opasich et al[51] and Kozdag et al[52] observed a prevalence of 18% and 21% respectively. The landmark study by Iervasi et al[66] involving 573 patients with heart disease found a prevalence of 30%. In India Zargar et al[67] studied sick euthyroid syndrome in chronic non-thyroidal illness and found a prevalence of 20.60%

STUDY	POPULATION	COUNTRY	PREVALENCE OF LOW T3 SYNDROME
Opasich et al	Chronic Heart Failure	Italy	18%
Iervasi et al	Patients with heart disease	Italy	30%
Zargar et al	Chronic non thyroid illness	India	20.60%
This study	Chronic Heart Failure	India	31.57%

Patients with Low total T3 values (T3<80ng/dl) had lower mean ejection fraction (29.2) than those with total T3 values of 80 ng/dl and above (34.78). This observation is consistent with the earlier study by Kozdag et al, who found that patients with Low T3 syndrome have lower ejection fraction.

We find advancing age, male sex, higher NYHA ciass, high left ventricular end diastolic diameter, lower ejection fraction, low total T3 and free T3 levels are associated with increased mortality. The mean total T3 levels and free T3 levels were lower in patients who died. Similar results were reported by Pingitore et al in their study on risk stratification in chronic heart failure, who found age, male sex, NYHA ciass, left ventricular end diastolic diameter, ejection fraction, total T3 and free T3 levels and obesity as significant univariate mortality predictors. However In our study, there was no significant association between obesity and mortality.

In a multivariate model with total T3, we find that Age, male sex, ejection fraction and total T3 are the significant predictors of increased mortality. In comparison, the study by Alessandro et al reported male sex, ejection fraction and total T3 as the multivariate predictors of increased mortality. We find advancing age is also a significant predictor of increased mortality, in contrast to the study by Pingitore et al[68].

We found a significant correlation of low total T3 levels with ejection fraction, indicating that patients who have low ejection fraction have low total T3 levels. Similarly Kozdag G et al found a significant correlation between low T3 values and reduced ejection fraction. This is in contrast to the study by Pingitore et al who did not find any correlation between low total T3 and ejection fraction.

We also found a significant correlation of low total T3 levels with advancing age. However, Pingitore et al reported no correlation between age and low T3 levels in a study.

From our analysis, we find that age, ejection fraction and total T3 levels are associated with increased mortality. Also, there is significant correlation of total T3 levels with age and ejection fraction. Hence, total T3 is an important predictor of mortality, but not the only predictor. Similarly, Opasich et al in a study on 199 chronic heart failure patients observed that Low T3 syndrome was not an independent negative prognostic factor but has a definite role when used with other parameters.

There is considerable diversity of opinions as to Whether T3 levels alone can be used to estimate mortality or not. Studies by Pingitore et al and Iervasi et al found T3 levels are independent predictors of mortality in patients with chronic heart failure. But Opasich et al and in this study we

find that Total T3 is significant but not the only parameter that estimates mortality.

In conclusion Total T3 levels are an important parameter in survival estimation of patients with chronic heart failure and should be used along with other conventional parameters like age and ejection fraction.

LIMITATIONS OF THE STUDY

Our study has the following limitations. We have studied patients with chronic heart failure following myocardial infarction. We have not included patients with chronic heart failure due to other causes. We could not estimate reverse T3 levels due to economic and practical reasons. In our study we measured thyroid profile at the base line and assessed its relationship to subsequent clinical events. However if thyroid hormone levels are measured frequently, its association with outcomes can be identified accurately.Correlation with important and established biomarkers like NT-proBNP ,CRP, etc was not done due to economic reasons.

CONCLUSION

CONCLUSION

- Thyroid function tests are significantly altered in patients with chronic heart failure.
- The prevalence of low T3 syndrome in chronic heart failure is 31.57%.
- Patients with low total T3 levels have lower ejection fraction and advanced NYHA class.
- Advancing age correlates with reduced total T3 levels.
- Total T3, ejection fraction and age are the most important predictors of mortality in this patient population.
- Total T3 levels can be used as an adjunct to other parameters for risk stratification and survival estimation in chronic heart failure.

SCOPE FOR FUTURE STUDIES

- Large-scale studies are needed to evaluation of the role of T3 hormone supplementation in chronic heart failure. If beneficial results could be demonstrated this could be a cost effective measure to reduce the high mortality associated with this condition.
- Frequent estimating thyroid hormone levels at various stages of heart failure can help in better understanding of the role of thyroid hormone in cardiovascular homeostasis.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017 Aug 8;136(6):e137-61.
2. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L: Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial StudyGroup.Circulation.Nov 1990; 82: 1730 –36
3. Iervasi G, Emdin M, Colzani RMP, et al: Beneficial effects of long-term triiodothyronine (T3) infusion in patients with advanced heart failure and low T3 syndrome. Washington, DC. Medimond Medical Publications; 2001: 549–553.
4. Hamilton MA, Stevenson LW, Fonarow GC: Safety and hemodynamic effects of intravenous triiodothyronine in advanced congestive heart failure. American Journal of Cardiology 1998; 81: 443–447

5. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology Eur. Heart J., June 1, 2005; 26(11): 1115 - 1140.

6. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol. 2001; 38:2101-13.

7. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health 1951; 41:279-286

8. Michael M. Givertz, Wilson S. Colucci, Eugene Braunwald: Clinical aspects of heart failure;Pulmonary edema, High output failure . In: Zipes, Libby, Bonow, Braunwald eds. Braunwald ‘s Heart Disease 2005; Chapter 22:540

9. He J, Ogden LG,Bazzano LA, et al : Risk factors for congestive heart failure in US men and women : NHANES I epidemiological follow-up study. Arch Intern Med 161:996,2001.

10. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation. 1982; 66:1146–1149

11. Rahimtoola SH. From coronary artery disease to heart failure: role of the hibernating myocardium. Am J Cardiol. 1995; 75:16E–22E

12. Levine TB, Francis GS, Gold smith SR, Simon AB , Cohn JN. Activity of the sympathetic nervous system and renin angiotensin system assessed by plasma hormonal levels and their relation to hemodynamic abnormalities in congestive heart failure: American journal of cardiology 1982; 49:1659-66

13. Hendry A,Hacking L,Langhorne P,Vallance R,MacDonald J.Evaluation of echocardiography in the management of elderly patients with heart failure. Age Ageing. 1999 Sep;28(5):447-50

14. Baker DW, Bahler RC, Finkelhor RS, Lauer MS: Screening for left ventricular systolic dysfunction among patients with risk factors for heart failure. American Heart Journal 2003 Oct; 146(4): 736-40

15. Sam Kaddoura. Heart failure, myocardium and pericardium. Echo made easy.2002, chapter 4:69-75

16. Rienzi A. Diaz, Petros Nihoyannopoulos, George Athanassopoulos Celia M.Oakley: Usefulness of echocardiography to differentiate

dilated cardiomyopathy from coronary-induced congestive heart failure. : American journal of cardiology 1991 Nov 1; 68(11): 1224-7.

17. Smart N,Haluska B, Leano R,Case C,Mottram PM,Marwick TH: Determinants of functional capacity in patients with chronic heart failure: role of filling pressure and systolic and diastolic function. American Heart Journal 2005 Jan; 149(1): 152-8

18. Weihs W, Anelli-Monti B, Schuchlenz H,Harb S: Practical assessmentusing transmitral Doppler echocardiography for the evaluation of left ventricular filling pressure in patients with systolic ventricular dysfunction Acta Medica Austriaca 1999;26(1):8-11.

19. Cohn JN, Johnson GR,Shabetai R, et al : Ejection fraction,peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias and serum norepinephrine as determinants of prognosis in heart failure. The V-HeFT VA Co operative Studies Group. Circulation 1993; 87: VI-5.

20. Berger R,Stanek B,Frey B , et al :B -type natriuretic peptides (BNP and PRO BNP) predict long term survival in patients with advanced heart failure treated with atenolol. Journal Of Heart Lung Transplant 2001; 20:251.

21. Iuliano S, Fisher SG, Karasik PE, et al: QRS duration and mortality in patients with congestive heart failure. American Heart Journal 2002; 143:1085-86.

22. Klingenheben T, Zabel M, D'Agostino RB, et al: Predictive value of T wave Alternans for arrhythmic events in patients with congestive heart failure. Lancet 2000; 356: 651-53

23. Hansen A,Haass M,Zugck C, et al: Prognostic value of Doppler echocardiographic mitral inflow patterns: Implications for risk stratification in patients with chronic congestive heart failure. Journal Of American College Of Cardiology 2001; 37: 1049-51

24. Hare JM, Johnson RJ: Uric acid predicts clinical outcomes in heart failure: Insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. Circulation 2003; 107:1951.

25. Tsutamato T, Hisanaga T, Wada A, et al: Interleukin 6 spill over in the peripheral circulation increases with severity of heart failure and the high plasma Interleukin 6 is an important prognostic predictor in patients with congestive heart failure. Journal Of American College Of Cardiology 1998; 31:391.

26. Tsutsui T, Tsutamato T, Wada A, et al: Plasma oxidized Low density lipoprotein as a prognostic predictor in patients with chronic

congestive heart failure Journal Of American College Of Cardiology 2002; 39:957

27. Francis GS, Cohn JN, Johnson G, et al: Plasma nor epinephrine, plasma renin activity and congestive heart failure. Relations tosurvival and the effects of therapy in V-HeFT II .The V-HeFT VA Co-operative Studies Group. Circulation 1993; 87: VI-40

28. May HT, Alharethi R, Anderson JL, Mulhestein JB, et al:

29. Homocysteine Levels Are Associated with Increased Risk of Congestive Heart Failure in Patients with and without Coronary Artery Disease. Cardiology. 2006 Aug; 107(3): 178-184

30. Sugimoto Y, Kinoshita M: Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: Prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventriculardysfunction.Circulation1997;96:509.

31. Klein I, Ojamaa K: Mechanisms of disease: thyroid hormone and the cardiovascular system. New England Journal of Med. 2001; 344:501-509, Feb 15, 2001.

32. Schmidt OTT, Ascheim DD: Thyroid hormone and heart failure.Curr Heart fail rep 2006 sep;3(3):114-9.

33. Tang YD,Kuzman JA,Said S,Anderson BE,Wang X,Gerdes AM. Low thyroid function leads to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles, and severe systolic dysfunction.Circulation.2005 Nov 15; 112(20): 3122-30.

34. Taddei S, Caraccio N, Virdis A et al :Impaired endothelium dependent vasodilatation in subclinical hypothyroidism: Beneficial effects of Levo thyroxine therapy. Journal Of Clinical Endocrinology And Metabolism 2003; 88:3731.

35. Parle JV, Maisonneuve P, Sheppard Mc, et al: Prediction of all-cause mortality and cardiovascular mortality in elderly people from one Low Thytropin result: A ten year cohort study. Lancet 2001; 358:861-63.

36. Carr AN, Kranias EG: Thyroid hormone regulation of calcium cycling proteins. Thyroid 2002; 12:253.

37. Ojamma K, Kenessey A, Klein I: Thyroid hormone regulation of Phospholamban phosphorylation in the rat heart. Endocrinology 2000; 141:2139-41.

38. Ronald J. Koenig Regulation of Type 1 Iodothyronine Deiodinase in Health and Disease Thyroid Aug 2005, Vol. 15, No. 8: 835 -840.

39. Lazarus, J H, Obuobie, K (2000): Thyroid disorders-an update. Postgrad Med J 76: 529-536

40. Carmine Zoccali, Giovanni Tripepi, Sebastiano Cutrupi et al: Low Triiodothyronine – A new facet of inflammation in end stage renal disease. Journal Of American Society Of Nephrology 2005; 16:2789-95

41. Elvio Cassia, Stefano Baglioni, Amir Eslami, et al: Low T 3 state – A predictor of outcome in respiratory failure: European Journal Of Endocrinology 2004; 151: 557-60

42. Pavlou HN, Kliridis PA, Panagiotopoulos AA, et al: Euthyroid sick syndrome in acute ischaemic syndromes. Angiology. 2002 Nov-Dec; 53(6): 699-707.

43. Vexiau P, Perez-Castiglioni P, Socie G, et al: 1993 The 'euthyroid sick syndrome': incidence, risk factors and prognostic value soon after allogeneic bone marrow transplantation. Br J Hematol 1993; 85:778–782.

44. Larry Jameson, Anthony P.Weetman: Disorders of the thyroid gland. In: Kasper, Braunwald eds. Harrison's Principles Of Internal Medicine 2005; Chapter 320:2119

45. McIver B, Gorman CA**.** 1997 Euthyroid sick syndrome: an overview. Thyroid. 7:125–132.

46. Fliers E, Guldenaar SE, Wiersinga WN, et al: Decreased hypothalamic thyrotropin releasing hormone gene expression in patients with non-thyroidal illness. Journal Of Clinical Endocrinology and Metabolism1997; 82:4032-6.

47. Harvey L. Katzeff, Saul R. Powell, and Kaie Ojamaa**:** Alterations in cardiac contractility and gene expression during low-T_3 syndrome: prevention with T_3. Am J Physiol Endocrinol Metab 1997; 273: E951-E956.

48. Langer P. The low triiodothyronine syndrome-the cause or the result of a critical state? , Bratisl Lek Listy. 1989; 90(7): 520-31.

49. Shanoudy H, Soliman A, Moe S, Hadian D, Veldhuis JD, Iranmanesh A, Russell DC. Early manifestations of "sick euthyroid" syndrome in patients with compensated chronic heart failure. J Card Fail. 2001 Jun; 7(2): 146-52

50. Pingitire A, Iervasi G, Barison A, Protera C et al :Early activation of an altered thyroid profile in asymptomatic and mildly symptomatic idiopathic left ventricular dysfunction. Journal of cardiac failure 2006; 12(7): 520-6

51. Opasich C, Pacini F, Ambrosino N,Riccardi PG,Febo O et al : Sick euthyroid syndrome in patients with moderate-to-severe chronic heart failure.European Heart Journal .1996 Dec;17(12):1860-6.

52. Kozdag G, Ural D, vural A, Agacdiken A: Relation between free triiodothyronine/free thyroxine ratio, echocardiographic parameters and mortality in dilated cardiomyopathy. European Journal Of Heart Failure 2005 Jan; 7(1): 113-8

53. Shimoyama N,Maeda T,inoue T,Niwa H,Saikawa T. Serum thyroid hormone levels correlate with cardiac function and ventricular tachyarrhythmia in patients with chronic heart failure. Journal of Cardiology .1993; 23(2): 205-13.

54. Hamilton MA, Stevenson LW, Luu M, Walden JA Altered thyroid hormone metabolism in advanced heart failure 1990 ; July16(1): 91-5.

55. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary artery bypass surgery. N Engl J Med. 1995; 333: 1522–1527

56. Moruzzi P, Doria E, Agostoni PG. Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. Am J Med 1996; 101:461-467.

57. Psirropoulos, D.; Lefkos, N.; Boudonas, G et al. Heart failure accompanied by sick euthyroid syndrome and exercise training. Current Opinion in Cardiology. 17(3): 266-270, May 2002

58. Spooner PH, Morkin E, Goldman S. Thyroid hormone and thyroid hormone analogues in the treatment of heart failure. Coron Artery Dis. 1999; 10: 395–9

59. Huwez FU,Houston AB,Watson J et al: Age and body surface area related normal upper and lower limits of M mode echocardiographic measurements and left ventricular volumes and mass from infancy to early adulthood.Br Heart J1994:72;276

60. J E Otterstad. Measuring left ventricular volume and ejection fraction with the biplane Simpson's method. Heart 2002; 88:559-560

61. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18:499-502.

62. Boston, Little, Brown: The criteria committee of the Newyork Heart association: Nomenclature and criteria for diagnosis of diseases of the heart and great vessels 9 th edition. 1994.

63. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation, Dec 2002**;** 106**:** 3143**.**

64. Care D. Standards of medical care in diabetes–2017: summary of revisions.

65. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama. 2014 Feb 5;311(5):507-20.

66. Iervasi G, Pingitore A,Landi P,et al:Low T3 syndrome – A Strong prognostic predictor of death in patients with heart disease. Circulation. 2003;107:708

67. Zargar AH, Ganie MA,Masoodi SR et al : Prevalence and pattern of sick euthyroid syndrome in acute and chronic non-thyroidal illness--

its relationship with severity and outcome of the disorder.. Pattern and prevalence of sick euthyroid syndrome in this part of the world. J Assoc Physicians India. 2004; Jan 52:27-31.

68. Pingitore A,Landi P,Taddei MC et al. Triiodothyronine levels for risk stratification of patients with chronic heart failure. American Journal of Medicine.2005;118(2):132-6

69. Ascheim DD, Hryniewicz K. Thyroid hormone metabolism in patients with congestive heart failure: the low triiodothyronine state. Thyroid. 2002 Jun 1;12(6):511-5.

70. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, L'abbate A, Donato L. Low-T3 syndrome. Circulation. 2003 Feb 11;107(5):708-13.

71. Brenta G, Thierer J, Sutton M, Acosta A, Vainstein N, Brites F, Boero L, Rosso LG, Anker S. Low plasma triiodothyronine levels in heart failure are associated with a reduced anabolic state and membrane damage. European journal of endocrinology. 2011 Jun 1;164(6):937-42.

72. Moruzzi P, Doria E, Agostoni PG. Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. The American journal of medicine. 1996 Nov 1;101(5):461-7.

73. Rothberger GD, Gadhvi S, Michelakis N, Kumar A, Calixte R, Shapiro LE. Usefulness of Serum Triiodothyronine (T3) to Predict Outcomes in Patients Hospitalized With Acute Heart Failure. The American journal of cardiology. 2017 Feb 15;119(4):599-603.

74. Huffman MD, Prabhakaran D. Heart failure: epidemiology and prevention in India. The National medical journal of India. 2010 Sep;23(5):283.

75. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. The Lancet Global Health. 2017 May 3.

ANNEXURES

ANNEXURE –I

PROFORMA

LOW T3 SYNDROME IN CHRONIC HEART FAILURE-PREVALENCE AND PROGNOSTIC SIGNIFICANCE

NAME:
AGE:
SEX:
OCCUPATION:
HEIGHT (METERS):
WEIGHT (Kg):
BODY MASS INDEX (Kg/m^2):

HISTORY OF PRESENTING ILLNESS:

1.DYSPNOEA	YES/NO
2.ORTHOPNEA	YES/NO
3.PND	YES/NO
4. FATIGUE	YES/NO
4.ANGINA	YES/NO
5.SYNCOPE	YES/NO
6.CYANOSIS	YES/NO
7.PALPITATIONS	YES/NO
8.COUGH	YES/NO
9.EXPECTORATION	YES/NO
10.PEDAL EDEMA	YES/NO

PAST HISTORY:

1.DIABETES	YES/NO (HOW MANY YEARS)
2.HYPERTENSION	YES/NO (HOW MANY YEARS)
3.MYOCARDIAL INFARCTION	DATE THROMBOLYSIS/PCI DURATION OF HOSPITALIZATION
4.ARRYTHMIAS	YES/NO
5.AMIODARONE	YES/NO (HOW MANY YEARS)
6.BETA-BLOCKER	YES/NO (HOW MANY YEARS)
7.ACE INHIBITOR	YES/NO (HOW MANY YEARS)
8.SMOKING	YES/NO (HOW MANY YEARS)
9.THYROID ILLNESS	YES/NO (HOW MANY YEARS)
10.ALCOHOL	YES/NO (HOW MANY YEARS)
11.ANY OTHER DRUGS/REMEDIES	

GENERAL EXAMINATION:

- CONSCIOUSNESS
- PALLOR
- TEMPERATURE
- CYANOSIS
- PEDAL EDEMA
- ICTERUS
- THYROID SWELLING

PULSE RATE: BLOOD PRESSURE:(STANDING&SUPINE)

JVP: TEMPERATURE :

SYSTEMIC EXAMINATION:

CARDIOVASCULAR SYSTEM:

MURMURS: YES/NO
LVH: YES/NO
RVH: YES/NO
S3: LV/RV YES/NO
NYHA CLASS (I-IV):

RESPIRATORY SYSTEM:

CREPITATIONS: YES/NO
PLEURAL EFFUSION: YES/NO

ABDOMEN

ASCITES: YES/NO
HEPATOMEGALY: YES/NO

CENTRAL NERVOUS SYSTEM:

INVESTIGATIONS:

1. COMPLETE BLOOD COUNT
   HEMOGLOBIN TOTAL COUNT
   DIFFERENTIAL COUNT ESR
   PLATELET COUNT

2. BLOOD UREA

3.BLOOD GLUCOSE FASTING 2hr POST PRANDIAL

4.SERUM CREATININE

5.SERUM ELECTROLYTES

6. FASTING SERUM CHOLESTEROL
TRIGLYCERIDES
LDL

VLDL

7.SERUM PROTEIN TOTAL
ALBUMIN
GLOBULIN

8.URINE ANALYSIS

9. CHEST X RAY CTR PLEURAL EFFUSION

10.ELECTROCARDIOGRAM
RATE
RHYTHM
P WAVE
P-R INTERVAL
QRS AXIS
QRS MORPHOLOGY
T WAVE
OTHERS

11.ECHOCARDIOGRAPHY
LEFT VENTRICLE END DIASTOLIC DIAMETER(LVEDD)
LEFT VENTRICLE END SYSTOLIC DIAMETER (LVESD)
EJECTION FRACTION (EF %)
LEFT ATRIAL ENLARGEMENT
MITRAL REGURGITATION
WALL MOTION ABNORMALITY
PULMONARY ARTERY PRESSURE
PERICARDIAL EFFUSION

12. THYROID PROFILE TSH
TOTAL T3
FREE T3
TOTAL T4
FREE T4

FOLLOW UP:

VISIT NUMBER:
COMPLAINTS:
DATE OF DEATH:
CAUSE OF DEATH:

ANNEXURE - II

PATIENT INFORMATION SHEET

We are conducting a study on **"LOW T3 SYNDROME IN HEART FAILURE: PREVALENCE AND PROGNOSTIC SIGNIFICANCE"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess thyroid dysfunction among patients with heart failure and its correlation with prognosis.

We are selecting certain cases and if you are found eligible, we may be using your clinical data, and collect blood samples to do certain tests which in any way do not affect your final report or management and perform a non invasive and painless 2D echocardiogram.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

ANNEXURE - III

PATIENT CONSENT FORM

Study Detail	:	"**LOW T3 SYNDROME IN HEART FAILURE : PREVALENCE AND PROGNOSTIC SIGNIFICANCE**"
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (√) these boxes

a) I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

b) I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

c) I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

d) I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

e) I hereby consent to participate in this study. ☐

f) I hereby give permission to undergo detailed clinical examination and blood investigations as required. ☐

Signature/thumb impression

Study Investigator's Name:

Patient's Name and Address:

Dr. SHARADHA S

ANNEXURE - IV

PLAGIARISM ANALYSIS

URKUND

Urkund Analysis Result

Analysed Document: LOW T3 SYNDROME IN CHRONIC HEART FAILURE.pdf (D31140826)
Submitted: 10/9/2017 11:41:00 AM
Submitted By: drsharadha08@gmail.com
Significance: 4 %

Sources included in the report:

https://stopthethyroidmadness.com/healthy-heart-with-t3/
http://www.thyroidmanager.org/chapter/adult-hypothyroidism/
https://link.springer.com/article/10.1007/s10741-008-9126-6
http://publicationslist.org/carminezoccali

Instances where selected sources appear:

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ANNEXURE - V

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **"LOW T3 SYNDROME IN CHRONIC HEART FAILURE : PREVALENCE AND PROGNOSTIC SIGNIFICANCE"** of the candidate **Dr. SHARADHA. S** with registration Number 107843 for the award of **DOCTOR OF MEDICINE** in the branch of General Medicine. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 1% percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal

Date :

Place:

ANNEXURE- VI

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr.Sharadha.S.,
Post Graduate in MD General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai 600 003

Dear Dr.Sharadha.S,

The Institutional Ethics Committee has considered your request and approved your study titled "**LOW T3 SYNDROME IN HEART FAILURE : PREVALENCE AND PROGNOSTIC SIGNIFICANCE "** - **NO.09012017 (II).**

The following members of Ethics Committee were present in the meeting hold on **19.01.2017** conducted at Madras Medical College, Chennai 3

1.Dr.C.Rajendran, MD.,	:Chairperson
2.Dr.M.K.Muralidharan,MS.,M.Ch.,Dean, MMC,Ch-3	:Deputy Chairperson
3.Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4.Prof.B.Vasanthi,MD., Prof.of Pharmacology.,MMC,Ch-3	: Member
5.Prof.A.Rajendran,MS, Prof. of Surgery,MMC,Ch-3	: Member
6.Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
7.Prof.Baby Vasumathi,MD.,Director, Inst. of O & G	: Member
8.Prof.K.Ramadevi,MD.,Director,Inst.of Bio-Che,MMC,Ch-3	: Member
9.Prof.R.Padmavathy, MD, Director,Inst.of Pathology,MMC,Ch-3	: Member
10.Prof.S.Mayilvahanan,MD,Director, Inst. of Int.Med,MMC, Ch-3	: Member
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary – Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

ANNEXURE VII

MASTER CHART

DIED

S.no	AGE	S	BMI	DM	HT	SM	TC	TG	HDL	LDL	B-B	EDD	EF	TSH	T T3	FT3	TT4	F T4	NYHA	Died at mnth
1	68	1	23.2	0	0	1	260	211	36	217	1	58	30	3.2	58	1.7	6.2	11	4	1
2	66	1	27.9	0	1	1	145	150	44	115	0	66	34	2.2	107	3.4	7.9	15	3	5
3	74	1	26.4	1	1	1	246	264	50	189	1	65	25	3.8	59	1.6	6.5	13	4	1
4	75	1	29	0	0	1	180	176	42	141	1	58	20	2.9	62	1.6	9.6	17	4	0
5	63	1	30.4	1	1	0	221	268	40	214	0	59	16	3.5	52	1.6	6.1	12	2	6
6	66	1	23.3	1	0	1	165	154	46	123	1	60	40	2.5	130	3.9	5.9	9.8	3	2
7	64`	1	26.2	0	0	0	190	190	42	152	0	66	32	1.9	76	2.2	7.3	14	4	0
8	63	1	29.3	0	0	1	136	154	55	105	1	69	24	3.3	54	1.7	5.8	12	3	1
9	68	1	30.8	1	1	1	179	169	48	145	1	75	22	3.6	53	1.4	7.6	16	4	5
10	64	1	27.5	1	1	1	298	210	24	256	0	58	34	3.3	130	3.9	9.5	17	3	6
11	66	1	26	0	1	0	195	162	45	163	1	65	30	2	68	1.6	6.2	11	4	1
12	63	1	25.4	0	0	1	187	153	42	156	1	67	32	3.5	51	1.1	5.9	13	2	3
13	64	1	22	1	1	0	194	146	47	165	0	64	24	1.5	78	2.2	8.6	18	3	4
14	62	1	28.4	0	0	1	176	196	50	137	1	60	32	3	100	2.7	5.3	12	4	0
15	62	1	31	1	0	1	178	198	42	138	1	61	30	3.8	52	1.4	7.9	15	3	1
16	59	1	27.1	0	1	0	234	290	20	176	0	64	26	3.7	58	1.6	7.6	15	4	0
17	70	1	26.3	1	0	1	178	155	48	147	0	76	18	2.6	78	2.2	7.9	15	3	4
18	63	1	22.6	0	0	0	169	189	43	131	1	58	30	3	61	1.5	6.9	15	3	2
19	69	1	26.7	0	1	1	290	198	28	250	1	57	34	3.1	138	3.9	6.9	15	1	6
20	67	1	23.5	0	0	0	149	150	49	119	0	62	40	1.1	70	1.5	8.4	16	3	5
21	69	1	26	1	0	0	187	166	44	154	1	63	32	0.9	73	1.9	5.3	11	4	3
22	57	1	27	0	0	0	197	154	50	166	0	64	28	2.8	75	2.1	7.2	14	3	5
23	66	2	32	0	1	0	190	310	35	128	1	66	18	3.8	63	1.1	11	18	4	4
24	69	2	26	0	0	0	190	156	55	159	0	74	30	2.5	74	1.9	5.8	11	4	2
25	70	2	23.8	1	0	0	186	180	48	150	0	65	36	2.6	66	1.7	9.1	17	3	3

ALIVE

	AGE	S	BMI	DM	HT	SM	TC	TG	HDL	LDL	B-B	EDD	EF	TSH	TT3	FT3	TT4	FT4	NYHA
1	59	2	31	0	1	0	265	220	35	210	0	57	34	3.6	110	3.3	6.5	11.9	4
2	60	2	33	0	1	0	186	154	58	155	1	59	40	3.5	126	3.6	5.4	9.5	2
3	57	2	26	1	0	0	241	266	40	188	1	60	38	3.3	109	3.2	7.6	15.2	3
4	64	2	26	0	1	0	310	298	26	250	1	56	30	2.4	117	3.5	9.6	16.2	4
5	71	2	28	0	0	0	234	290	20	176	1	59	32	1.9	149	4	6.1	13.4	4
6	64	2	28	0	1	0	198	189	54	160	1	66	40	3.3	171	3.7	12	17.6	2
7	53	2	31	0	0	0	296	180	40	260	0	67	36	3.6	181	3.9	7.3	14.3	1
8	59	2	23	1	1	0	192	198	48	152	1	58	38	3.6	51	1.6	5.4	9.6	4
9	56	2	31	0	0	0	260	165	45	227	1	60	34	0.9	99	3.1	12	17.6	2
10	65	2	31	1	0	0	250	150	40	220	1	68	36	2.6	98	2.8	11	16.9	4
11	49	2	26	0	1	0	230	190	35	192	0	56	40	3.1	136	3.1	6.2	13.9	2
12	51	2	25	0	1	0	190	150	41	160	1	58	35	2.4	70	2	6.6	12.5	2
13	50	2	23	0	0	0	154	146	48	125	1	59	30	3.2	143	3.4	6.6	14.7	4
14	63	2	32	1	1	0	190	256	45	139	0	58	32	0.8	129	3.7	12	15.5	2
15	66	2	29	1	0	0	187	146	42	158	1	60	36	1.3	145	3.8	7.9	15.7	3
16	54	2	31	0	0	0	290	198	30	250	1	61	38	0.8	98	3.3	7.6	14.9	2
17	59	2	27	1	1	0	181	175	42	144	0	58	36	3.2	128	3.7	5.8	7.8	3
18	56	1	32	0	0	1	210	220	45	166	0	57	40	2.2	66	1.8	11	17.2	1
19	55	1	31	1	1	1	243	197	40	104	1	60	40	3.8	87	2.7	10	15.2	4
20	58	1	25	0	1	1	174	187	50	137	0	66	36	2.9	158	3.9	8.4	14.6	2
21	60	1	24	1	0	1	260	168	36	226	1	63	32	3.5	182	4	5.3	7.6	3
22	62	1	23	0	1	0	190	169	30	156	0	61	36	2.4	130	2.9	9.1	14.7	2
23	59	1	25	1	0	1	186	198	43	146	1	61	35	1.9	155	3.7	11	17.5	4
24	52	1	31	0	1	0	210	159	44	178	0	57	30	3.4	163	4.2	5.8	12.6	2
25	51	1	24	0	0	1	190	167	45	157	0	59	28	3.6	145	3.4	9.5	12.9	4

	AGE	S	BMI	DM	HT	SM	TC	TG	HDL	LDL	B-B	EDD	EF	TSH	TT3	FT3	TT4	FT4	NYHA
26	50	1	31	1	1	0	245	240	35	197	1	60	34	2.2	172	3.8	8.7	16.9	2
27	60	1	25	1	0	1	300	198	25	260	1	66	36	2	149	3.7	6.8	12.2	4
28	55	1	25	0	0	1	176	164	54	143	1	60	36	3.1	170	4	7.4	15.9	2
28	54	1	24	0	1	1	230	178	40	194	0	58	38	2.3	138	4.1	6.9	14.6	1
30	58	1	27	0	1	1	224	159	45	192	1	61	40	3.3	130	3.9	9.5	17	2
31	60	1	26	1	0	1	187	104	40	166	1	61	30	2.8	75	1.9	8.7	16.6	3
32	58	1	26	0	1	0	197	137	50	170	0	60	36	3.6	180	3.4	5.9	8.4	2
33	55	1	30	0	1	1	166	178	36	131	1	57	35	3.9	150	3.8	6.1	14.7	3
34	61	1	31	0	0	1	290	298	24	231	1	59	28	2.9	162	3.5	6.6	15.5	4
35	53	1	31	1	1	1	220	146	30	191	0	58	20	2.4	144	3.7	7.3	14.9	2
36	52	1	23	0	1	0	190	158	30	159	1	66	40	1.9	177	3.9	5.8	12.2	4
37	55	1	24	0	0	1	279	145	35	250	1	65	32	2.5	94	2.8	7.6	16.1	2
38	58	1	25	0	1	0	145	132	48	119	0	69	34	3.6	173	3.8	11	17.2	3
39	57	1	28	1	0	1	240	154	46	209	1	64	36	2.2	164	4	6.2	11.2	2
40	69	1	26	0	1	1	190	177	42	155	0	59	20	2.6	139	3.6	5.8	13.3	4
41	70	1	31	0	0	1	176	167	30	143	0	63	30	0.9	124	3.7	8.7	15.9	2
42	72	1	28	1	1	0	156	123	50	131	1	68	40	2	147	3.8	8.1	15.4	3
43	59	1	25	0	0	1	310	220	35	266	0	60	28	3.5	120	2.4	7.9	14.9	3
44	76	1	30	0	1	1	190	198	52	159	1	59	34	1.5	126	3.1	7.7	13.8	2
45	55	1	24	1	0	1	230	180	40	194	0	60	32	1.9	142	3.8	7.9	15.2	2
46	54	1	27	1	0	1	197	178	42	161	1	57	40	3.8	139	3.9	6.9	15.2	4
47	57	1	26	0	0	1	188	167	44	155	1	66	38	3.7	129	2.8	8.6	16.6	2
48	57	1	31	1	1	1	254	165	45	221	0	65	30	2.6	111	3.6	8.5	17.4	4
49	60	1	28	0	0	0	154	109	53	132	1	61	28	1.9	69	1.9	8.2	15.9	4
50	52	1	31	1	0	1	229	190	30	191	0	60	32	2.8	94	3	9.1	14.8	4
51	50	1	26	0	0	1	163	178	46	127	1	57	36	3.5	85	2.5	11	16.5	3

1-yes
2-no
S = sex, 1=male, 2= female

KEY TO MASTER CHART

S	Sex
BMI	Basal metabolic rate
DM	Diabetes Mellitus
HT	Hypertension
SM	Smoking
TC	Total cholesterol
TG	Triglycerides
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
B-B	Beta Blocker use
EDD	End Diastolic Dimension
EF	Ejection Fraction
TSH	Thyroid Stimulating Hormone
TT3	Total T3
TT4	Total T4
FT3	Free T4
FT4	Free T4
NYHA	New York Heart Association

Sex : 1- Male
2- Female

1- yes
0- No